VOLUME 37 DECEMBER 1, 1972 NUMBER 24 JOCEAH

# THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

# THE JOURNAL OF Organic Chemistry

*Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania*




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

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistants, ANDREW J. D'AMELIO and DEBORAH K. MILLER.

Advertising Office: Centcom, Ltd. (formerly Century Communication Corporation), 142 East Ave., Norwalk, Conn. 06851.



### Business and Subscription Information

Correspondence concerning business matters should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue plus time normally required for postal delivery of journal and claim; (2) if loss was due to failure to notify the Subscription Service Department of a change of address; or (3) if the reason for the claim is that a copy is "missing from files."

Change of address: Notify Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Such notification should include both old and new addresses and postal ZIP number. Please send an old address label, if possible. Allow 4 weeks for change.

Subscriptions should be renewed promptly, to avoid a break in your series. Orders should be sent to the Subscription Service Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

Subscription rates for 1972: $20.00 per volume to members of the ACS and $60.00 per volume to all others. Those interested in becoming members should write to the Admissions Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Add $5.00 per subscription for Canada and countries belonging to the Postal Union, and $6.00 for all other countries.

Single copies for current year: $3.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

This publication and the other ACS periodical publications are now available on microfilm. For information write to MICROFILM, Special Issues Sales Department, 1155 Sixteenth St., N.W., Washington, D. C. 20036.

*Notice to Authors last printed in the issue of August 11, 1972*

**AMERICAN CHEMICAL SOCIETY,** *1155 Sixteenth Street, N.W., Washington, D. C. 20036*

**BOOKS AND JOURNALS DIVISION**

JOHN K CRUM
*Director*

JOSEPH H. KUNEY
*Head, Business Operations Department*

RUTH REYNARD
*Assistant to the Director*

JOCEAH 37(24) 3755-3974 (1972)

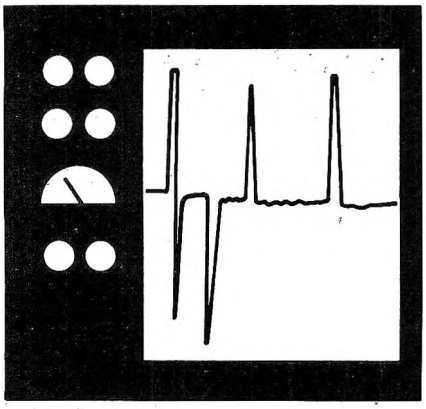
THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 24 DECEMBER 1, 1972

# Pesticides Identification
## at the Residue Level

ADVANCES IN CHEMISTRY SERIES No. 104

*Ten papers from a symposium by the Division of Pesticide Chemistry of the American Chemical Society chaired by Francis J. Biros.*



Pesticides—key to abundance or the beginning of the end? Whether their use leads to more abundant production or to a "silent spring" could well depend on the development and use of analytical techniques. Residues of pesticides and their derivatives have been reported throughout the world and blamed for endangering countless forms of life. Which is actually at fault—the pesticides or the analytical techniques? Some of the topics examined are:

- gas–liquid chromatographic detectors
- infrared and ultraviolet spectrophotometry
- thin-layer and paper chromatography
- mass spectrometry
- neutron activation analysis
- biological assay methods

182 pages with index Cloth (1971) $8.50
Postpaid in U.S. and Canada; plus 40 cents elsewhere.
Set of L.C. cards with library orders upon request.

## Other books in the ADVANCES IN CHEMISTRY SERIES on pesticides include:

**No. 86 Pesticidal Formulations Research. Physical and Colloidal Chemical Aspects**
Fifteen papers survey contact angle of surface-active agents, transport through a membrane, vapor pressure of pesticides, role of surfactants in sprays, biological activity, evaporation, spray formation and drift, and several studies on specific pests and pesticides.
212 pages with index Cloth (1969) $9.50

**No. 60 Organic Pesticides in the Environment**
Gives a clear perspective of environmental hazards in soil, water, and air; surveys effects of mammal enzyme systems, residues in human body tissues, effects of chronic poisoning by organophosphorus insecticides.
309 pages with index Cloth (1966) $10.50

**No. 53 Natural Pest Control Agents**
Plants and animals produce agents which can control life processes in insects or other plants. Twelve papers survey such known agents as repellants in arthropods; insecticides in pyrethrum and cruciferous crops; insect toxicants in bacteria; virus and growth regulators in plants.
146 pages with index Cloth (1966) $7.00

**No. 41 New Approaches to Pest Control and Eradication**
Surveys the "silver bullet" approaches in insect eradication, including male annihilation, chemosterilants, anti-feeding agents, bacterial disease, and sex attractants.
74 pages Paper (1963) $5.00

**No. 13 Pesticides in Tropical Agriculture**
Use of pesticides on basic tropical food crops—sugar cane, cotton, cacao, rubber, coffee, rice, and bananas—in weed control and on stored products.
102 pages Paper (1955) $5.00

Order from:
**Special Issues Sales**
**American Chemical Society**
**1155 16th St., N.W., Washington, D.C. 20036**

**NOTES**

## COMMUNICATIONS



## AUTHOR INDEX



In papers with more than one author the name of the author to whom inquiries about the paper should be addressed is marked with an asterisk in the by-line.

THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 24

DECEMBER 1, 1972

# Novel Syntheses of 1,4-Benzodiazepines, Isoindolo[2,1-*d*][1,4]benzodiazepines, Isoindolo[1,2-*a*][2]benzazepines, and Indolo[2,3-*d*][2]benzazepines, Based on Use of the Strecker Reaction

GORDON N. WALKER,* ALLAN R. ENGLE, AND ROBERT J. KEMPTON

*Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901*

*Received May 30, 1972*

Strecker reactions of *N*-alkylanilines and *o*-aminobenzophenones **10a**, **23**, and **29** (R′ = $CH_3$) gave corresponding glycinonitriles, which were hydrogenated in the presence of activated nickel catalyst and $NH_3$ to give *N*-arylethylenediamines. Condensation products of **2** with phthalaldehydic acid undergo novel PPA cyclization to **4**, which are reducible with $LiAlH_4$ to **5**, whereas similar compounds **8** are converted with $LiAlH_4$ to fused hydroxyphthalimidines **9**. Keto nitrile **24** underwent catalytic hydrogenation (Ni) followed by cyclization to the known benzodiazepine **25**. Facile closure of **24** into cyanoindole **26a** followed by reduction gave the 2-aminomethylindole **26c**; such compounds have been transformed previously into benzodiazepin-2-ones **27** by oxidative ring opening and reclosure. Similar reduction of keto nitrile esters **33** leads to compounds **35**, whereas base-catalyzed cyclization of **33** gives cyanoindoles **36**, which are converted by reduction and cyclization into benzazepinones **39**. Various derivatives of secondary amino keto nitrile **12a** and oximino nitrile **18a** were prepared; **18b** and **18c** are relays on a new path to **15**. Reaction of α- (**10b**) and β- (**10c**) amino oximes with HCHO gave **14** and **13**, respectively. Amino keto esters **29** (R′ = $CH_3$) were obtained by esterifying acids resulting from ring opening of morphanthridine-6,11-diones **28**. Spiro compounds **31** and **34** were obtained by reaction of acids **29** (R′ = H) with HCHO and action of bases on bromoacetylamino acids **32**, respectively. Hydroxy dilactams **35a,b** were obtained from bromoacetylamino esters **32** (R′ = $CH_3$) with ammonia. Reactions leading from **35a,b** to **37** and **38** were found. Compound **35c** was hydrogenolyzed over Pd to **4a**.

1,4-Benzodiazepines have been studied intensively in the last decade.[1,2] However, little or no work has been directed toward synthesis of appropriately ortho-substituted anilinoacetonitriles and derived amines $ArN(R)(CH_2)_2NH_2$ as precursors of 1,4-benzodiazepines. The closure of an *o*-$N(R)CH_2COOR$-substituted benzhydrylamine to a 3-oxo-1,4-benzodiazepine has been reported.[3]

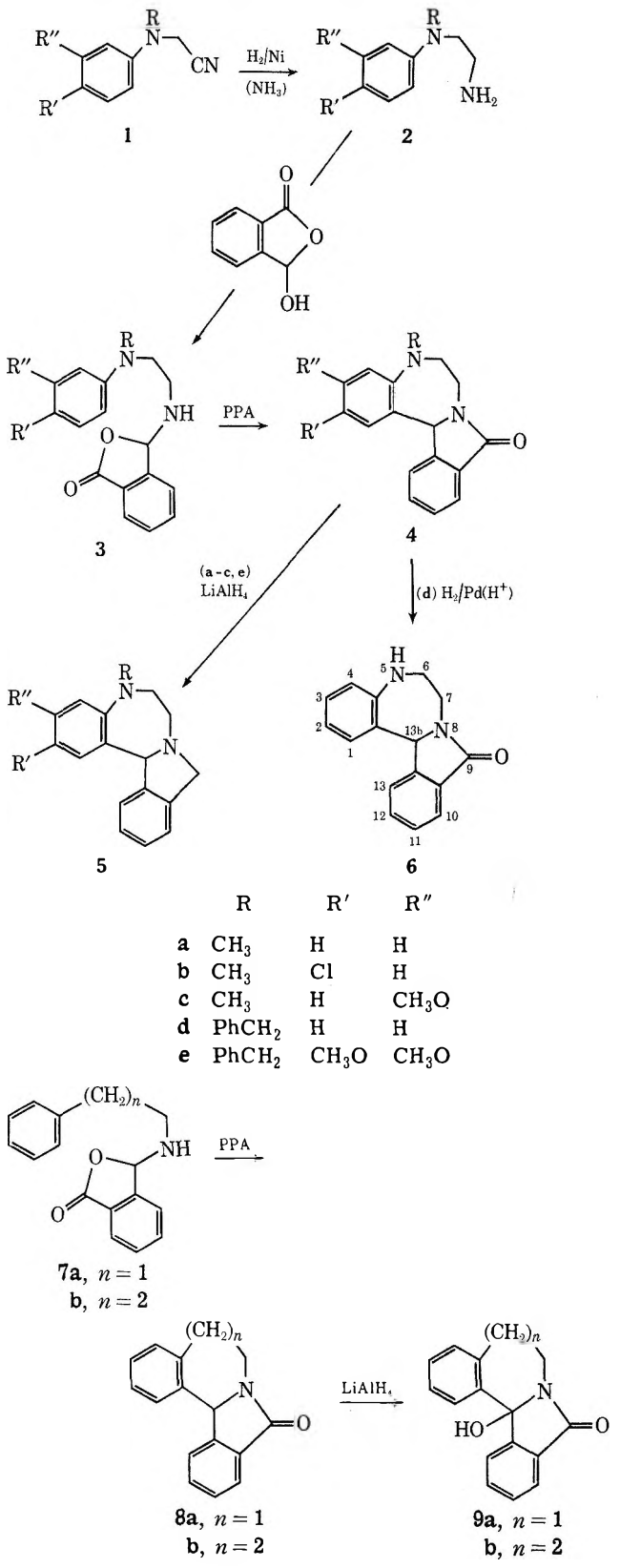
Anilines have been alkylated with α-halo esters[3] and nitriles,[4] but such reactions are difficult, particularly with weakly nucleophilic anthranilic acid and *o*-aminobenzophenone relatives. Possible approaches to introduction of an *N*-β-aminoethyl group on anilines by use of ethylene oxide, ethyleneimine, or *N*-β-bromoethylphthalimide[5] have their individual difficulties. A simple process, applicable under mild conditions and without complications to a relatively wide variety of anilines, was desired. We now report modifications of the Strecker condensation of anilines with formaldehyde and cyanide.[6-10]

In general, it was found that the so-called Knoevenagel–Bucherer method,[7] involving sequential use of formaldehyde bisulfite to prepare the water-soluble $ArN(R)CH_2SO_3^-\ Na^+$ followed by treatment with aqueous KCN to form water-insoluble anilinonitriles, is a reliable route to *N*-arylglycinonitriles from aniline, *p*-chloroaniline, aminoveratrole, and their simple *N*-alkyl derivatives. However, neither this procedure nor that used by Itoh[8] and others (starting from the aniline hydrochloride) worked as desired with less soluble *N*-benzylanilines or with weakly basic anilines ortho or para substituted by carbonyl or similar groups. For Strecker reaction in these cases, the methods devised by Marxer[9] and Dimroth,[10] using an acetic acid medium, were found to serve best.

An equally useful means for reduction of many anilinoacetonitriles to *N*-aryl ethylenediamines was found in low-pressure, nickel-catalyzed hydrogenation in ethanol in the presence of excess ammonia. Given a sufficiently active catalyst, one need not employ high pressure[8] or temperature in such reductions.

(1) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 751 (1968).
(2) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).
(3) G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1967); *Chem. Abstr.*, **65**, 16988 (1966).
(4) G. S. Sidhu, G. Thyagarajan, and M. Mazharuddin, *Indian J. Chem.*, **2**, 170 (1964).
(5) S. Gabriel, *Ber.*, **22**, 2225 (1889).
(6) D. T. Mowry, *Chem. Rev.*, **42**, 230 (1948).
(7) R. I. Buchanan and R. A. Partyka, U. S. Patent 3,517,024 (1970); *cf.* E. Knoevenagel, *Ber.*, **37**, 4059 (1904); W. M. Lauer and C. M. Langkammerer, *J. Amer. Chem. Soc.*, **57**, 2360 (1935); T. D. Stewart and C.-H. Li, *ibid.* **60**, 2782 (1938).
(8) N. Itoh, *Chem. Pharm. Bull.*, **10**, 55 (1962).
(9) A. Marxer, *Helv. Chim. Acta*, **37**, 166 (1954).
(10) K. Dimroth and H. G. Aurich, *Ber.*, **98**, 3902, 3907 (1965).

SCHEME I




| | R | R′ | R″ |
|---|---|---|---|
| a | $CH_3$ | H | H |
| b | $CH_3$ | Cl | H |
| c | $CH_3$ | H | $CH_3O$ |
| d | $PhCH_2$ | H | H |
| e | $PhCH_2$ | $CH_3O$ | $CH_3O$ |

**7a**, $n = 1$
**b**, $n = 2$

**8a**, $n = 1$
**b**, $n = 2$

**9a**, $n = 1$
**b**, $n = 2$

**Synthesis of Seven-Membered Rings by Pictet–Spengler Closure of β-Anilinoethylamine Derivatives (Scheme I).**—With adequate quantities of diamines **2** on hand from reduction of Strecker nitriles **1**, we found a novel synthetic approach to dihydroisoindolo[2,1-*d*]-[1,4]benzodiazepines. Some representatives of this ring system had already been synthesized;[11] however, we had found earlier[12] that the condensation product of phthalaldehydic acid with β-phenylethylamine, **7a**, could be cyclized with PPA to fused lactam **8a**. This observation has been extended to similar synthesis of fused benzazepine and benzodiazepine rings. Condensation of diamines **2** with equivalent amounts of phthalaldehydic acid in benzene gave crude products apparently consisting (like **7a**)[12] mainly of the aminophthalides **3** (ir 5.70 μ), but probably containing also certain amounts of *N*,*N*-bis-3-phthalidyl aminoethylanilines[13] and small amounts of hydroxyphthalimidines.

Crude **3a** was cyclized with PPA at 100° to **4a** in 36% yield. Comparable yields of **4b**,**c**,**e** were obtained similarly from corresponding compounds **3**. The closure of **3d** gave a 65% yield of **4d**.

The related cyclization of **7b** to the isoindolo[1,2-*a*]-[2]benzazepine **8b** was also carried out with PPA with a longer period of heating at 100°.

These ring closures, like others of the type, presumably represent the nucleophilic attack of an aromatic ring carbon of sufficient electron density on an acyliminium moiety of sufficient reactivity. The latter originates in the very reactive phthalaldehydic acid system. During the closure of **3** to **4**, the aniline nitrogen evidently is not protonated by PPA to an extent which would suffice to obliterate the nucleophilicity of the ortho position; in the somewhat similar Meisenheimer closure of mandelylanilines to oxindoles, the fact that the nitrogen is acylated provides a similar effect. The closure to **4** fails when R = H or R = Ac in **3** because different pathways involving direct reaction of aniline N with the phthalaldiminium moiety are followed.

Ring closures of other amides, the phthalimide, homophthalimide, phenylacetamide, and α-cyanoacetamide, prepared from **2a**, with PPA or PPE at 100–200° were tried, without success.

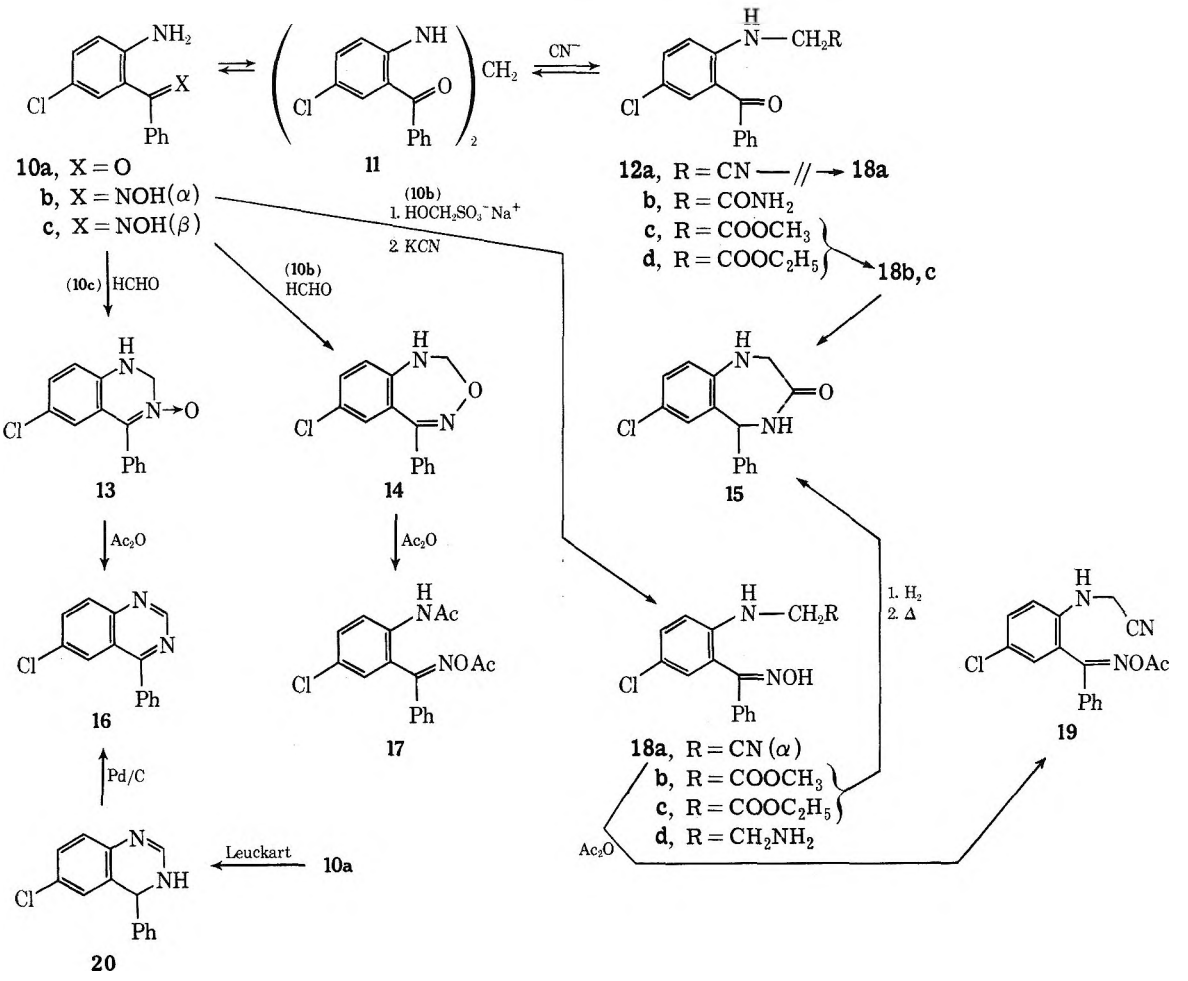
**Strecker Nitriles Derived from Primary *o*-Aminobenzophenones (Scheme II).**—Preliminary efforts to convert aminonitriles of this type to 2,3-dihydro-1*H*-1,4-benzodiazepines *via* reduction to diamines were not successful, but relay routes to 4,5-dihydro-1*H*-1,4-benzodiazepin-3-ones were found. The Dimroth modification of the Strecker reaction[10] was applicable to preparation of the new nitrile **12a** from the very weakly basic 2-aminobenzophenone **10a**. Slight deviations from the procedure given led to formation of the bis-aminomethylene compound **11**. Reaction of **11** with KCN in the presence of $Ac_2O$ gave a mixture of **12a** and **21a**. The CN is a rather efficient leaving group in **12a**, since the latter reverted to **11** with ammonia and to **11** or **10b**,**c** with hydroxylamine. Amide **12b** was prepared in low yield by performing the Strecker reaction on **10a** with aqueous HCHO and KCN. Esters **12c** and **12d** could be obtained by carefully esterifying **12a**.

(11) G. E. Hardtmann and H. Ott, *J. Org. Chem.*, **34**, 2244 (1969); U. S. Patents 3,375,246 (1968); 3,465,042 (1969); 3,475,449 (1969); 3,558,648 (1971); *cf.* W. J. Houlihan, U. S. Patent 3,428, 650 (1969).

(12) G. N. Walker and R. J. Kempton, *J. Org. Chem.*, **36**, 1413 (1971). The reaction of **8a** with $LiAlH_4$ to give mainly **9a** is described in the Experimental Section of that paper.

(13) Y. Kubota and T. Tatsuno, *Chem. Pharm. Bull.*, **19**, 1226 (1971).

SCHEME II



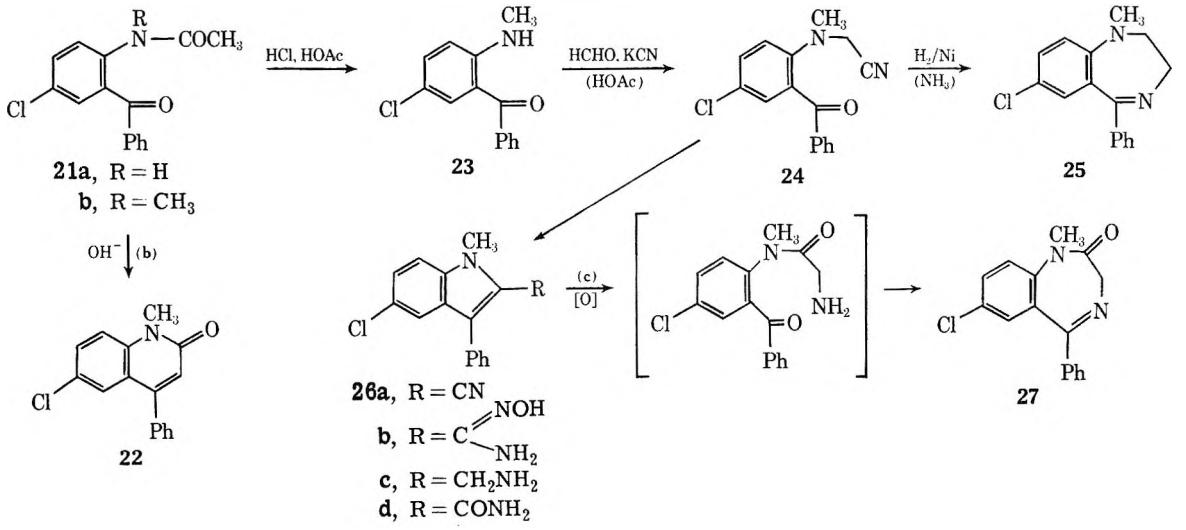

Reactions of α- and β-oximes[14,15] **10b** and **10c** with formaldehyde itself gave entirely different results. The α-oxime gave the colorless 3,1,4-benzoxadiazepine **14**, a novel compound of a class containing relatively few representatives.[14-16] The β-oxime with HCHO itself or $HOCH_2SO_3^-Na^+$ gave the yellow 1,2-dihydroquinazoline 3-oxide **13**,[17] a member of a group of compounds[18,19] which, together with 3,4-dihydro-4-arylquinazolines,[20-22] has received attention principally in connection with benzodiazepine syntheses. Interestingly, formation of **13** also was observed when **12a** and **14** were exposed to hydroxylamine and KCN, respectively. The structure of **13** was confirmed by quantitative $Ac_2O$-promoted Polonovski oxidation and elimination to give the quinazoline **16**, identical with a sample prepared by facile aromatization of **20**.

Strecker reaction of the β-oxime obviously was out of the question. However, using formaldehyde bisulfite on the α-oxime **10b** with DMF to dissolve the intermediate, followed by KCN treatment, we found that **18a** could be prepared. The oximino aminonitrile **18a** did not lose its CN group so readily as did **12a**. Esterification of **18a** was a more efficient route to **18b,c** than was reaction of **12c,d** with hydroxylamine. Compounds **12d** and **18c** are the same as those obtained[3] starting with the difficult $BrCH_2COOEt$ alkylation of **10a**. Compound **18c** is reported[3] to have been converted, *via* reduction to amino ester and thermal closure, to lactam **15**.

Attempts to promote intramolecular reaction under acidic conditions (HOAc, HCl, HBr) of nitrile and oximino groups in **18a** in the sense described by Taylor[23] were unrewarding, as indeed might be anticipated from the conversion of **18a** to corresponding esters **18b,c** in alcoholic HCl media. Unfortunately, the β isomer of **18a** is not available at present. However the relevant record of base-induced, retrograde reactions and ring contractions in 3-oxo-, 3-oxy-, and 3-amino-3*H*-1,4-benzodiazepines[22,24-30] may be cited in this regard.

(14) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960).
(15) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).
(16) W. Metlesics, G. Silverman, and L. H. Sternbach, *Monatsh. Chem.*, **98**, 633 (1967); *Chem. Abstr.*, **67**, 82198 (1967).
(17) G. F. Field and L. H. Sternbach, South African Patent 6,707,098 (1968); *Chem. Abstr.*, **70**, 96817 (1969).
(18) G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Lett.*, 2609 (1966); U. S. Patent 3,523,972 (1970); *J. Org. Chem.*, **36**, 777, 2968 (1971).
(19) S. C. Bell, U. S. Patent 3,509,148 (1970).
(20) M. Denzer and H. Ott, *J. Org. Chem.*, **34**, 183 (1969); H. Ott, U. S. Patent 3,531,474 (1970).
(21) G. N. Walker, U. S. Patents 3,560,501 (1971), 3,646,028 (1972); *Chem. Abstr.*, **70**, 106556 (1969); M. H. Sherlock, U. S. Patent 3,466,284 (1969).
(22) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
(23) E. C. Taylor and K. Lenhard, *J. Amer. Chem. Soc.*, **90**, 2424 (1968).
(24) S. C. Bell, C. Gochman, and S. J. Childress, *ibid.*, **28**, 3010 (1963).
(25) S. C. Bell and S. J. Childress, *ibid.*, **29**, 506 (1964).
(26) W. Metlesics, G. Silverman, and L. H. Sternbach, *ibid.*, **29**, 1621 (1964).
(27) S. C. Bell and P. H. L. Wei, *ibid.*, **30**, 3576 (1965).
(28) R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *ibid.*, **36**, 1064 (1971).
(29) A. Walser, G. Silverman, J. Blount, R. I. Fryer, and L. H. Sternbach, *ibid.*, **36**, 1465 (1971).
(30) P. N. Giraldi, A. Fojanesi, G. P. Tosolino, E. Dradi, and W. Logeman, *J. Heterocycl. Chem.*, **7**, 1429 (1970).

SCHEME III




**Strecker Nitriles Derived from Secondary *o*-Aminobenzophenones, and Their Conversion to Indoles and Dihydro-5-aryl-2*H*-1,4-benzodiazepines (Scheme III).**—Glacial acetic acid again was used in the reaction of the *N*-methylaminobenzophenone **23** with paraformaldehyde and KCN, to give nitrile **24** in good yield. In contrast with **12a**, nitrile **24** did not lose $CN^-$ readily, and was reduced smoothly in the presence of activated nickel catalyst and ammonia. The resulting amino ketone formed the cyclic imine *in situ*, giving the known dihydro-1,4-benzodiazepine **25**, upon which much interest has focused,[31,32] in 75% yield.

Reactions of the relatively stable **24** with various nucleophiles differed from those of labile **12a**. With amines, alkoxides, and other bases, keto aminonitrile **24** underwent facile cyclization to indole **26a** in high yield. Although the keto group of *o*-aminobenzophenones is notoriously unreactive, this internal Claisen reaction apparently is highly favored sterically. Also, when the amino group is tertiary as in **24**, the methylene adjacent to CN may more readily form an anion, and not revert to methyleneiminium + $CN^-$ as it tends to do with an NH present. A rather similar closure of *o*-carbalkoxymethoxy benzophenones with bases to 3-aryl-2-carbalkoxybenzofurans was noted previously.[33]

Cyclization of **24** to **26a** also took place in the presence of dry HCl. The first step in this reaction may be protonation on oxygen, as in vinylogous amides in general; sterically favored nucleophilic attack of methylene on the benzhydrylium ion and dehydration would follow.

With hydroxylamine as the base, there was again facile ring closure, giving the indole amidoxime **26b**, identical with that prepared from **26a** with $H_2NOH$. The nitrile group in **26a** was found to be inert to electrophilic reagents (HCl, PPA) but quite susceptible to nucleophilic attack and to hydrogenation. Nickel-catalyzed reduction of **26a,b** in the presence of ammonia readily gave the amine **26c**. This compound is identical with one of a number of 2-aminomethyl-3-arylindoles prepared by Japp–Klingemann synthesis from arylhydrazines of 3-aryl-2-carbalkoxyindoles, conversion to 2-carbonitriles, and reduction.[34] Compound **26c** and related 2-aminomethylindoles have in turn been oxidatively opened ($O_3$ or $CrO_3$) and the intermediate amino keto amides reclosed to 1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-ones[34] such as **27**. Thus our investigation of nitriles **12a**, **18a**, and **24** ended with a relay to **27**.

It may be noted that at this point new synthetic routes to four types of known compounds, **4**–**6**, **15**, **25**, and **27**, of interest in pharmaceutical chemistry, had been found.

**Tetracyclic Benzodiazepines and Benzazepines from *o*′-Aminobenzoylbenzoic Acid Derivatives (Scheme IV).**—A functional group ortho′ on appended phenyl may be envisioned as potentially useful in conjunction with moieties generated by the ring closures of Scheme III for the synthesis of tetracyclic compounds. Morphanthridine-6,11-diones **28** are prepared by Schmidt and other ring expansions of anthraquinones, and from them a number of 11-hydroxy and 11-amino morphanthridin-6-ones are available.[11,35–39] The well-recognized ring opening of the 6,11-diones to *o*′-aminobenzoylbenzoic acids,[40] and of corresponding 6-on-11-ols to 3-*o*′-aminophenylphthalides,[36,41] has been extended somewhat by Ott[11] to synthesis of certain 1-*o*′-aminophenylisoindolines from 11-aminomorphanthridin-6-ones. The problem in further use of *o*′-aminobenzoyl-

(31) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456, 3013 (1963); *Arzneim. Forsch.*, **18**, 1542 (1968); U. S. Patent 3,553,199 (1971); L. Tamayo, Spanish Patent 356,713 (1970); *Chem. Abstr.*, **73**, 3946 (1970).

(32) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963).

(33) G. N. Walker and R. T. Smith, *ibid.*, **36**, 305 (1971). See also M. Oklobdžija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

(34) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Ber.*, **101**, 4245 (1968); S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **17**, 1263 (1969); **19**, 263,722 (1971); U. S. Patent 3,557,092 (1971); see also *Chem. Abstr.*, **71**, 124519, 124521 (1969); **74**, 3672, 22904, 88075, 88076, 88081, 88086 (1971). See also M. Oklobdžija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

(35) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **2**, 276 (1965); **3**, 206 (1966); and references cited therein.

(36) F. Hunziker, F. Künzle, and J. Schmutz, *Helv. Chim. Acta*, **49**, 1433 (1966), and references cited therein.

(37) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).

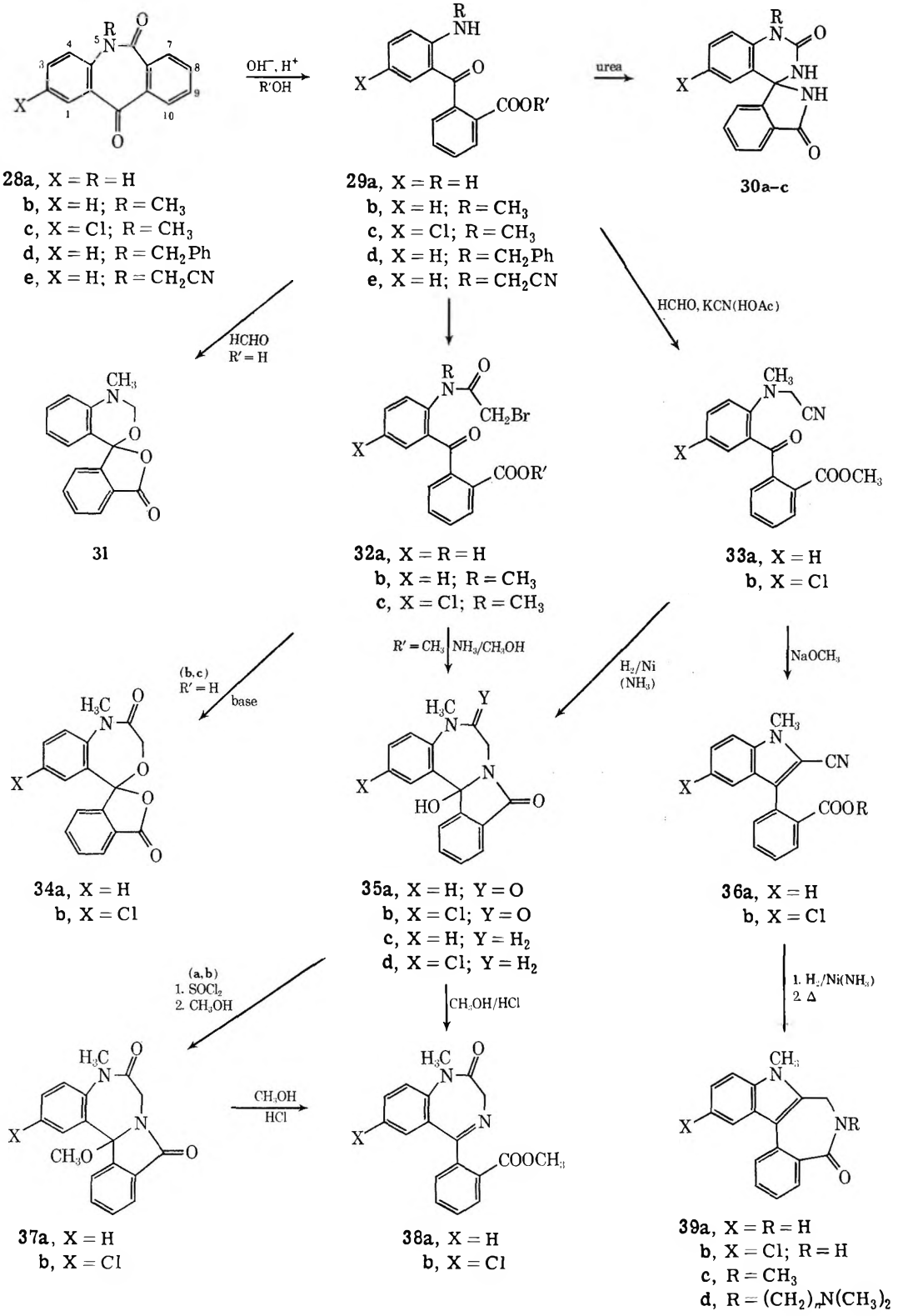
(38) W. S. Waring, U. S. Patent 3,242,167 (1966); *Chem. Abstr.*, **62**, 10422 (1965).

(39) G. N. Walker, U. S. Patents 3,471,473 (1969); 3,504,088, 3,530,219 (1970); 3,632,572, 3,652,550 (1972).

(40) D. D. Emrick and W. E. Truce, *J. Org. Chem.*, **26**, 1329 (1961).

(41) J. O. Jílek, J. Pomykáček, E. Savátek, V. Seidlová, M. Rajšner, K. Pelz, B. Hoch, and M. Protiva, *Collect. Czech. Chem. Commun.*, **30**, 445 (1965).

SCHEME IV




**28a**, X = R = H
**b**, X = H; R = $CH_3$
**c**, X = Cl; R = $CH_3$
**d**, X = H; R = $CH_2Ph$
**e**, X = H; R = $CH_2CN$

**29a**, X = R = H
**b**, X = H; R = $CH_3$
**c**, X = Cl; R = $CH_3$
**d**, X = H; R = $CH_2Ph$
**e**, X = H; R = $CH_2CN$

**30a–c**

**31**

**32a**, X = R = H
**b**, X = H; R = $CH_3$
**c**, X = Cl; R = $CH_3$

**33a**, X = H
**b**, X = Cl

**34a**, X = H
**b**, X = Cl

**35a**, X = H; Y = O
**b**, X = Cl; Y = O
**c**, X = H; Y = $H_2$
**d**, X = Cl; Y = $H_2$

**36a**, X = H
**b**, X = Cl

**37a**, X = H
**b**, X = Cl

**38a**, X = H
**b**, X = Cl

**39a**, X = R = H
**b**, X = Cl; R = H
**c**, R = $CH_3$
**d**, R = $(CH_2)_nN(CH_3)_2$

benzoic acids lies in preventing their relatively facile reclosure to morphanthridin-6-ones.

We found a very useful and apparently not previously suspected fact: ring-opened amino acids **29** (R′ = H) are esterified almost quantitatively on standing with a large excess of methanolic HCl, giving amino keto esters **29** (R′ = $CH_3$). This provided an opening for new work in the field, albeit esters **29** on fusion with urea give the same type of spiro compounds **30** as have been obtained from **28** with urea.[42]

With HCHO (in attempted Strecker reactions) the acid **29b** (R′ = H) gave spiro compound **31** through reaction of the *N*-methylol with the *o*-benzoylbenzoic acid moiety, whereas the Strecker reaction (in HOAc)

(42) S. Palazzo, *Gazz. Chim. Ital.*, **96**, 1641 (1966); *Chem. Abstr.*, **67**, 32673 (1967).

on corresponding esters **29** (R′ = $CH_3$) gave desired amino keto ester nitriles **33**. Related findings were made with bromoacetyl acids and esters **32** (R′ = H and $CH_3$, respectively). On attempting to displace Br with $NH_3$ or other amines in **32** (R′ = H), the ring tautomeric carboxylate ion apparently functioned as the nucleophile, resulting in formation of novel spiro compounds **34**. However, the Br was replaced normally with $NH_3$ in methanol[43] in esters **32** (R′ = $CH_3$), and interaction of the side chain $NH_2$ group with the keto ester led as expected[44] to the tetracyclic hydroxyphthalimidines **35a,b**. Similarly, nickel-catalyzed reduction of nitriles **33**, in the presence of $NH_3$, generated an amino group which interacted with the keto ester moiety in the same way, giving **35c,d**, albeit in rather low yields.

Compounds **35**, novel inasmuch as isoindolo[2,1-*d*][1,4]benzodiazepines at so high a level of oxidation had not been synthesized previously, underwent some quite interesting transformations. With warm, methanolic HCl, **35a** was solvolytically ring opened and dehydrated to the *o*′-carbomethoxy-2*H*-1,4-benzodiazepin-2-one **38a**, a type of compound previously mentioned in passing but not actually prepared.[45] The acid imine hydrochloride corresponding to **38a** was obtained by treatment of **35a** with dry HCl in the absence of methanol. Performing similar operations on the 2-chloro analog **35b**, one learned that the 13b position is influenced electronically by the 2-chloro substituent in a more or less predictable sense (*i.e.*, vinylogously similar to an $\alpha$-chloro C=O moiety). On short exposure to warm MeOH–HCl, **35b** gave the 13b-methoxy compound **37b**, and on longer exposure to the same reagent either **37b** or **35b** afforded **38b**. Formation of 3-alkoxyphthalimidines under rather different circumstances has been observed previously.[44] The des-2-chloro-13b-methoxy compound **37a** was not obtained similarly, but was prepared by treatment of **35a** with thionyl chloride and then methanol.[44]

To obtain compounds corresponding to **35a,b** with NH in place of the *N*-methyl group at position 5, it was planned originally to proceed *via* **32** with R = benzyl; therefore **28d** and **29d** (R′ = H and $CH_3$) were prepared. Later, however, **32a** (R′ = $CH_3$) from bromoacetylation of **29a** (R′ = $CH_3$) was found to give **35a** (H in place of $CH_3$) directly with $NH_3$ in methanol.

Secondary aminonitriles **29e** (R′ = H and $CH_3$) were obtained by carefully opening **28e** to a potassium salt, followed by acidification or methylation ($CH_3I$); however, neither these nor **28e** itself gave recognizable products on nickel reduction, and like the compounds of Scheme II were not converted into indoles.

Strecker nitriles **33**, like **24**, were converted by $NaOCH_3$ in methanol to indoles **36**, with accompanying solvolysis to corresponding acids (R = H), a fact which speaks for the probable intervention of lactonic (ring tautomeric carboxylate) derivatives of intermediate ketols. Acids **36** having been reesterified to corresponding esters **36** (R = $CH_3$), hydrogenation in the presence of nickel and $NH_3$ was found to give (as with **26a** → **26c**) corresponding 2-aminomethylindoles. These were closed readily to lactams **39a,b**, which represent a ring system not previously synthesized, the indolo[2,3*d*][2]benzazepines, and which, like other 2-benzazepin-1-ones,[46] are alkylated by usual techniques, *e.g.*, to **39c,d**.

**Hydride Reductions and Hydrogenolyses in Isoindolo[2,1-*d*][1,4]benzodiazepines.**—In our earlier work[12] lithium aluminum hydride reduction of **8a** (Scheme I) was found to be anomalous, giving mainly **9a**. We find that reaction of **8b** with $LiAlH_4$ similarly gives almost exclusively the fused hydroxyphthalimidine **9b**, rather than the cyclic tertiary amine. Presumably these reactions proceed to fused isoindoles, which undergo autooxidation during work-up, leading to **9**. In the light of this information, it was rather surprising to find that compounds **4**, with a basic rather than a neutral atom at position 5, are reduced normally with $LiAlH_4$ to the fused isoindolines **5**.

This difference may be explained by assuming that, in **4**, it is (vinylogously) as though nitrogen atom 5 were attached directly to position 13b, electronically inhibiting the loss of proton 13b along with 9-hydroxy of a presumed, intermediate carbinolamine to form an isoindole.

In synthesizing 6,7-dihydro-13b*H*-isoindolo[2,1-*d*][1,4]benzodiazepin-6-ones and the 6,9-diones by a different approach, Hardtmann and Ott[11] evidently encountered *de novo* the anomalies long known to attend the preparation of 1-phenylisoindolines by reduction of phthalimidines, and were obliged to resort to electrolytic reduction of phthalimidines or Zn/HOAc reduction of isoindoles in preparation of their intermediate isoindolines. It is also relevant to note that they did not report any $LiAlH_4$ reductions of their 6-oxo analogs of **4**. We find similarly that compounds **35** (Scheme IV) cannot be reduced with $LiAlH_4$ to recognizable products.

On the other hand, acid-catalyzed hydrogenolysis (Pd) of 5-benzyl and 13b-hydroxy groups in compounds such as **4** and **35** proceeds normally. Thus **4d** HCl was converted to **6**. Hydroxy lactams **35a,c**, as well as 5-desmethyl **35a**, were hydrogenolyzed with Pd/C in warm HOAc to give corresponding 13b-desoxy lactams. The hydrogenolysis of **35c** gave **4a**, identical with that prepared by cyclization of **3a**, providing a welcome confirmation of structures of tetracyclic lactams prepared by quite different routes.

## Experimental Section

Melting points (uncorrected) were obtained using a Thomas-Hoover silicone oil bath; ir spectra (Nujol mulls unless otherwise noted) were taken on a Perkin-Elmer 21 double beam instrument; uv curves (MeOH solutions) were measured with a Cary 14 recording spectrophotometer; mass spectra were recorded using a MS-902 double-focusing apparatus; nmr spectra were obtained with a Varian A-60, $Me_4Si$ internal standard.

***N*-Methylanilinoacetonitrile (1a).**—To a solution of 110 g (1.06 mol) of sodium bisulfite in 300 ml of water was added 36% formalin (88 g, 1.06 mol), and 10 min later there was added 106 g (1.00 mol) of *N*-methylaniline. The mixture was heated on a steam cone and stirred vigorously for 0.8 hr; the hot solution

(43) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, S. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962); J. Iacobelli, M. Uskokovic, and W. Wenner, *ibid.*, **27**, 3606 (1962); **29**, 582 (1964); *J. Heterocycl. Chem.*, **2**, 323 (1965); U. S. Patent 3,244,698 (1966); C.-M. Lee, *J. Heterocycl. Chem.*, **1**, 235 (1964); R. G. Grict, U. S. Patent 3,414,563 (1968); N. Blažević and F. Kajfež, *J. Heterocycl. Chem.*, **7**, 1173 (1970); **8**, 845 (1971).

(44) W. Graf, E. Girod, E. Schmidt, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959), and references cited therein.

(45) E. Reeder and L. H. Sternbach, U. S. Patent 3,109,843 (1963).

(46) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).

was treated with a concentrated aqueous solution of 65 g (1.00 mol) of KCN and heated for 0.5 hr longer. After cooling, the oil was extracted with ether. The washed (water, two portions) and dried ($K_2CO_3$) ether solution was evaporated and the crude oil (136 g) was distilled *in vacuo* to give 109 g (75%) of oil, bp 86–91° (0.4–0.5 mm) [lit.[8] bp 105–110° (2 mm)], ir 4.48 μ (very weak).

Nitriles **1b** and **1c** were prepared by a similar Knoevenagel–Bucherer–modified Strecker technique,[7] from appropriate precursor *N*-methylanilines, as follows.

**Nitrile 1b. A.**—N-Methylation of 113 g of *p*-chloroacetanilide (mp 178°; prepared from *p*-chloroaniline with $Ac_2O$) with excess $CH_3I$ (100 ml) in the presence of NaH (30 g, 56%) in DMF (700 ml), evaporation on a steam cone (1 hr), treatment with water, and extraction with ether gave 78 g (63%) of *N*-methyl-*p*-chloroacetanilide, mp 78–84°.[47]

**B.**—Hydrolysis of 75 g of the acetyl derivative (A) with 40 g of NaOH ln 175 ml of water and 200 ml of ethanol (6 hr reflux) and isolation of the amine by extraction with 15% HCl and treatment with NaOH solution, gave 50 g of *p*-chloro-*N*-methylaniline as an oil.

**C. Strecker Reaction.**—Sodium bisulfite solution (47 g, 0.45 mol, in 300 ml of water) and 36% formalin (38 g, 0.45 mol) were combined, crude *p*-chloro-*N*-methylaniline (50 g, 0.35 mol) was added, the suspension was stirred at 90° for 1.5 hr, and the aqueous solution was decanted from residual brown oil and treated with a concentrated aqueous solution of 32 g (0.49 mol) of KCN. After heating at 70–80° for 0.5 hr, the cooled suspension was extracted with ether, and the ether solution was washed with water, dried ($K_2CO_3$), and evaporated, yielding 35 g (51%) of **1b** as an oil, 88% pure by gpc, ir 4.46 μ (barely discernible).

The nitrile was characterized by preparation of the corresponding amidoxime dihydrochloride, as follows. To a solution of 0.7 g of Na in 250 ml of ethanol was added 2.1 g of $H_2NOH \cdot HCl$ and 5.35 g of nitrile. After refluxing for 1 hr, the filtered, evaporated, and refiltered ethanol solution of base was treated with dry HCl to give colorless crystals: mp 195–196° (from EtOH); ir 2.93, 3.16, 5.95, and 6.28 μ; uv 252 nm (ε 18,210) and 300 (1860); $FeCl_3$ test, deep red.

*Anal.* Calcd for $C_9H_{12}ClN_3O \cdot 2HCl$: C, 43.22; H, 5.24; N, 16.80. Found: C, 43.06; H, 5.24; N, 16.44.

**Nitrile 1c. A.**—N-Methylation of 114 g of *m*-methoxyacetanilide[48] with $CH_3I$ in the presence of 34 g of 56% NaH in DMF gave 46 g of *N*-methyl-*m*-methoxyacetanilide: mp 67–68° (from ligroin); ir 6.03 μ; uv 274 nm (ε 2380) and 281 (2190).

*Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.39; H, 7.48; N, 7.89.

**B.**—Hydrolysis of 40 g of material from A with 40 g of NaOH in 300 ml of aqueous EtOH (4 hr reflux), dilution and extraction with ether, reextraction with dilute HCl, and regeneration of the base (NaOH) afforded 29 g of crude *m*-methoxy-*N*-methylaniline as a purplish oil, suitable for further work: ir 2.94 μ; uv 207 nm (ε 32300), 246 (9060), and 290 (2590).

**C. Strecker Reaction.**—Combining 28.5 g of $NaHSO_3$ in 200 ml of water with 25 ml of formalin (36%), then adding crude amine from B and warming on a steam cone for 1 hr with stirring, resulted in solution of nearly all the material. The warm solution was filtered clear, diluted with 200 ml of water, treated with 22 g of KCN, and heated gently on a steam cone for 20 min. The oily product, after cooling, was extracted with ether, and the ether solution was washed three times with water, dried over $K_2CO_3$, and evaporated to give 21.5 g of crude **1c**: ir virtually devoid of NH peak, CN band barely visible; uv 210 nm (ε 33,740), 246 (9910), and 286 (2650). The material was suitable for use without purification.

***p*-Chloroanilinoacetonitrile.**—Following the literature procedure,[7] using 0.53 mol each of $NaHSO_3$ and HCHO and 64 g (0.50 mol) of *p*-chloroaniline in 500 ml of water, heating on a steam cone, and stirring for 0.6 hr, there was obtained 0.50 mol of $p\text{-}ClC_6H_4NHCH_2SO_3^-Na^+$, which is sparingly soluble in water and crystallizes from the aqueous solution on cooling: mp *ca.* 265° dec; ir 2.81, 2.93, 6.12, and 6.27 μ. The solution was diluted with 500 ml of additional water, reheated, treated with an aqueous solution of 42 g of KCN, and heated on a steam cone, for 1.5 hr. The product crystallized on cooling and was collected washed with water, and air dried: yield 48 g of crystals; mp 57–63° (95% pure by gpc), raised on recrystallization from ether–ligroin to mp 66–67.5° (lit.[7] mp 66.5–68°); ir 2.95 (strong) and 4.45 μ (very weak); uv 246 nm (ε 16,630) and 298 (1840).

*Anal.* Calcd for $C_8H_7ClN_2$: C, 57.66; H, 4.24; N, 16.82. Found: C, 57.33; H, 4.41; N, 16.60.

Additional material, obtained on addition of more KCN and further (4 hr) heating of the aqueous solution remaining from the foregoing reaction, proved not to be more nitrile, but rather a by-product, *p*-chloroanilinoacetamide: crystals from ether; mp 129–131°; ir 2.94, 3.03, 3.17, 5.98, and 6.08 μ; uv 249 nm (ε 16,920) and 302 (1900).

*Anal.* Calcd for $C_8H_9ClN_2O$: C, 52.04; H, 4.91; N, 15.18. Found: C, 52.11; H, 5.29; N, 14.85.

The *N*-acetyl derivative of the aminonitrile was prepared by heating a sample with excess $Ac_2O$ at 100° or reflux (1 hr): colorless crystals from ether; mp 72–73°; ir 4.47 (very weak) and 5.99 μ; uv 224 nm (ε 10,760) and 260 (330).

*Anal.* Calcd for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.35; N, 13.43. Found: C, 57.72; H, 4.35; N, 13.30.

The *p*-chloro-*N*-acetylanilinoacetonitrile (5.6 g) was also converted to the corresponding amidoxime by 1-hr reflux in an ethanolic (250 ml) solution of hydroxylamine (prepared using 0.6 g of Na and 1.85 g of $H_2NOH \cdot HCl$): yield 5.2 g of crystals from EtOH; mp 175–177°; ir 2.89, 2.98, 3.12, 6.00, and 6.14 μ; uv inflection 220 nm (ε 13,170); $FeCl_3$ test deep red or green.

*Anal.* Calcd for $C_{10}H_{12}ClN_3O_2$: C, 49.69; H, 5.01; N, 17.39. Found: C, 49.44; H, 4.93; N, 17.03.

***N*-Benzylanilinoacetonitrile (1d).**—Glacial acetic acid (200 ml) was added with stirring to a mixture of 26.8 g (0.146 mol) of *N*-benzylaniline, 9 g (0.30 mol) of paraformaldehyde, and 19.5 g (0.30 mol) of KCN. The materials dissolved in *ca.* 10 min, the temperature rising to *ca.* 50°. After stirring for 2 hr, the solution was added to 1.2 l. of water and the resulting oil was extracted with ether. The washed ($NaHCO_3$ solution, water) and dried ($K_2CO_3$) ether solution was evaporated, and the oil was distilled *in vacuo:* 11.2 g (35%); bp 141–145° (0.3 mm); 94% pure by gpc; ir nearly devoid of NH, 4.48 μ (barely visible).

***N*-Benzyl-4-veratrylaminoacetonitrile (1e)** was obtained by similar Dimroth-modified Strecker reaction from a suitable precursor prepared as follows.

**A. 4-*N*-Benzylideneveratrole.**—A solution of 15.3 g of 4-aminoveratrole and 11 g of benzaldehyde in 200 ml of benzene was refluxed under a water trap for 1.5 hr and evaporated to give 25 g of crude, crystalline imine: mp 54–55° after recrystallization from cyclohexane; ir 6.18–6.28 μ; uv 256 nm (ε 18,910) and 339 (12,230).

*Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.81. Found: C, 74.90; H, 6.35; N, 5.70.

**B.**—$NaBH_4$ was added in excess to 25 g of imine (A) in methanol (200 ml) and after 2 hr the MeOH was evaporated, the residue was treated with water, and the product was extracted with ether; the water-washed and dried ($K_2CO_3$) solution gave on evaporation 23 g of crude 4-*N*-benzylveratrole as an oil.

**C. Strecker Reaction.**—To a mixture of 22.6 g (0.093 mol) of amine from B, 8.4 g (0.28 mol) of paraformaldehyde, and 18.2 g (0.28 mol) of KCN was added 140 ml of glacial acetic acid, and the suspension was warmed to 50–60° periodically (four or five times) while stirring, over the course of 4.5 hr. The cooled solution was diluted with 1 l. of water, and the oil was extracted with ether–ethyl acetate, washed with 5% $NaHCO_3$ solution and water, dried ($K_2CO_3$), and evaporated to give 26 g of crude crystals yielding on trituration with ether 19 g of product, mp 81–84°. Recrystallization from ether gave colorless crystals: mp 86–87°; ir 6.20–6.25 μ (CN peak scarcely visible); uv 207 nm (ε 37,130), 245 (11,270), and 294 (3110).

*Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.30; H, 6.33; N, 10.05.

A sample (4.2 g) of the nitrile was converted by 2-hr reflux with 170 ml of ethanolic $H_2NOH$ (from 0.95 g of Na and 2.8 g of $H_2NOH \cdot HCl$) to the corresponding amidoxime (3 g). Recrystallization from aqueous ethanol, then benzene, gave, as the hydrate, colorless crystals: mp 91–96°; ir 2.91, 3.01, and 6.01 μ; uv 249 nm (ε 12,150) and 303 (4460); $FeCl_3$ test red.

*Anal.* Calcd for $C_{17}H_{21}N_3O_3 \cdot H_2O$: C, 61.24; H, 6.95; N, 12.61. Found: C, 60.80; H, 6.90; N, 12.38.

**Hydrogenation of Nitriles 1 to *N*-(2-Aminoethyl)anilines 2.**—The reduction procedure may be exemplified by preparation of *N*-(2-aminoethyl)-*N*-methylaniline (**2a**). To 250 ml of ethanol saturated with $NH_3$ at room temperature was added 27.6 g

(47) *Cf.* R. Stoermer and P. Hoffmann, *Ber.*, **31**, 2523 (1898); F. D. Chattaway and K. J. P. Orton, *J. Chem. Soc.*, **79**, 461 (1901).

(48) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

(0.19 mol) of nitrile **1a** and 1–2 parts by weight of moist, water- and alcohol-washed W. R. Grace 28 activated nickel catalyst. The suspension was shaken under hydrogen at 45–50 lb initial gauge pressure (Parr apparatus; 4-l. reserve tank) at room temperature for 5 hr. A pressure drop of 30 lb gauge, nearly complete in 3 hr, indicated uptake of $2H_2$. The catalyst was filtered and the solution was evaporated to give 26.7 g of diamine as a pale yellow oil, sufficiently pure for further work, ir 2.98–3.0 $\mu$.

It was found to be preferable to distil nitrile **1a** and use crude diamine **2a** as obtained directly from the reduction, rather than attempt to purify **2a** by distillation, as serious losses resulted in the latter procedure; in one run, crude **2a** (80% pure by gpc) from apparently complete reduction of 132.7 g of crude nitrile **1a** on distillation gave only 68.1 g (50% overall yield) of **2a**, bp 62–66° (0.1–0.3 mm) [lit.[8] bp 94–97° (2 mm)].

A sample of the corresponding dihydrochloride was prepared as colorless crystals (from methanol), mp 205–208° dec, ir 4.09 $\mu$ (very broad).

*Anal.* Calcd for $C_9H_{14}N_2 \cdot 2HCl$: C, 48.44; H, 7.23; N, 12.56. Found: C, 48.80; H, 7.37; N, 12.45.

Diamines **2b–e** were prepared from corresponding precursors **1** by the same procedure. Occasionally it was necessary to recharge with fresh catalyst in order to achieve smooth reduction (**2b,c**) of crude nitriles, and in some instances (**2c,e**) the crude diamine was taken into ether, washed with water, and dried ($K_2CO_3$) and the solvent was reevaporated, in order to obtain materials suitable for further work.

**Compound 2b** (90% pure by gpc) was characterized as the corresponding hydrochloride: crystals from EtOH, mp 252–255° dec; uv 257 nm ($\epsilon$ 19,260) and 306 (1840).

*Anal.* Calcd for $C_9H_{13}ClN_2 \cdot HCl$: C, 48.88; H, 6.38; N, 12.67. Found: C, 48.79; H, 6.41; N, 12.88.

**Compound 2c** was an oil: ir broad $NH_2$ band; uv 211 nm ($\epsilon$ 29,690), 251 (11,580), and 294 (2910) Like **2c** it formed a dihydrochloride as crystals (from EtOH): mp 178–181° dec; uv 211 nm ($\epsilon$ 32,380), 248 (12,060), and 290 (2930). Exact analytical figures could not be obtained. Similar results were observed with **2d** 2HCl.

**Compound 2e** was characterized as the dihydrochloride: crystals from ethanol–ether; mp 194–196° dec; ir 4.31 $\mu$ (broad, with side bands); uv 249 nm ($\epsilon$ 10,240) and 302 (2800).

*Anal.* Calcd for $C_{17}H_{22}N_2O_2 \cdot 2HCl$: C, 56.83; H, 6.73; N, 7.80. Found: C, 56.74; H, 6.80; N, 7.45.

**2-(3-Phthalidylamino)ethylanilines 3.**—Each of these intermediates was prepared by a facile azeotropic condensation: a solution of 0.1 mol each of the appropriate arylalkylaminoethylamine **2** and *o*-carboxybenzaldehyde in 150–200 ml of benzene was refluxed under a water separator for 1–2 hr, an amount of water corresponding closely to theory being trapped. Evaporation of the resulting solutions gave viscous oil in each case, having a strong ir 5.7-$\mu$ peak and frequently a weaker 5.91-$\mu$ band. The crude products were used *per se* in cyclizations, without undue delay. Some of the materials, notably crude **1a** and **1b**, tended to crystallize partly on standing; it was futile to attempt fractionation, as small crystalline fractions isolated by various triturations on several occasions proved not to be samples of compounds **3** but rather impure samples of by-products.

**5-Methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-9-(13b*H*)-one (4a).**—Cyclization of compounds **3** to tetracyclic lactams **4** was carried out typically as follows. A mixture of 20 g of crude **3a** and 300 g of PPA was stirred and heated in a steam bath for 0.7 hr. The resulting deep green solution was cooled and added with stirring to 1600 ml of ice–water. In the case of **4a** it was necessary to convert the $H_3PO_4$ solution to a buffered medium by addition of cold, aqueous NaOH to bring about complete separation of crude product; in the remaining examples **4b–e** this was not necessary. The crude material was collected (**4a,d,e**) or extracted with ether (**4b,c**), and washed with water. An ether, ether–ethyl acetate, or benzene solution of the crude material was washed with successive portions of 2% NaOH solution and water, dried ($Na_2SO_4$), and evaporated. Trituration of the semicrystalline residue afforded 6.8 g (36%) of **4a** as crystals, mp 143–148°. Recrystallization from ether and methanol gave a pure sample: mp 145–148°; ir 5.92 $\mu$; uv 250 nm ($\epsilon$ 12,640) and 280 (4230); nmr ($CDCl_3$) $\delta$ 8.1–6.9 (m, 8, ArH), 5.9 (s, 1, methine), 3.2–4.1 (m, 4, methylenes), and 2.98 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.41; H, 6.26; N, 10.56.

**Compound 4b** was obtained from similar cyclization of **3b** in 34% yield: crystals (from ether); mp 140–141°; ir 5.88–5.93 $\mu$; uv 257 nm ($\epsilon$ 13,180) and inflection 300 (2480); nmr ($CDCl_3$) $\delta$ 8.2–6.9 (m, 7, ArH), 5.88 (s, 1, methine), 3.2–4.1 (m, 4, methylenes), and 2.98 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.41; H, 5.39; N, 9.35.

**Compound 4c** was obtained from **3c** in 27% yield: crystals (from methanol); mp 132–134°; ir 5.95 $\mu$; uv 220 nm ($\epsilon$ 37,820), inflection 248 (13,190), 279 (4400), and inflection 291 (2870); nmr ($CDCl_3$) $\delta$ 7.96 (q, 1, proton 10), 7.7–7.4 (m, 3, protons 11, 12, and 13), 6.88 (d, 1, $J$ = 8 Hz, proton 1), 6.67 (d, 1, $J$ = 2.2 Hz, proton 4), 6.43 (q, 1, $J_{ortho}$ = 8 $J_{meta}$ = 2.2 Hz, proton 2), 5.84 (s, 1, methine), 4.2–3.2 (m, 4, methylenes), 3.8 (s, 3, $OCH_3$), and 2.96 (s, 3, NCH).

*Anal.* Calcd for $C_{18}N_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.76; H, 6.33; N, 9.53.

**Compound 4d** was obtained from **3d** with PPA after 1.5 hr: yield 65%; initially obtained crystalline by tlc; crystals from ether; mp 116–119°; ir 5.89 $\mu$; uv 249 nm ($\epsilon$ 13,120) with inflection at 228 (15,580) and 280 (4460); nmr ($CDCl_3$) $\delta$ 8.1–6.8 (m, 13, ArH), 6.0 (s, 1, methine), 4.44 (q, 2, $J_{AB}$ = 14 Hz, benzyl $CH_2$), 3.8–2.8 (m, 4, methylenes).

*Anal.* Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.86; H, 6.05; N, 8.12.

**Compound 4e** was obtained from **3e** with PPA after 0.5 hr: yield 43%; crystals from ethanol; mp 157–158°; ir 5.93 $\mu$; uv 250 nm ($\epsilon$ 14,950), inflection at 279 (4680), and 297 (4460); nmr ($CDCl_3$) $\delta$ 7.94 (q, 1, proton 10), 7.7–7.2 (m, 8, $C_6H_5$ and protons 11, 12, and 13), 6.77 (s, 1, proton 1), 6.55 (s, 1, proton 4), 6.0 (s, 1, methine), 4.42 (q, 2, $J_{AB}$ = 13 Hz, benzyl $CH_2$), 4.0–2.8 (m, 4, methylenes), with 3.88 (s, 3, $OCH_3$) and 3.64 (s, 3, $OCH_3$).

*Anal.* Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 75.18; H, 6.00; N, 7.12.

**5-Methyl-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine (5a).**—Reduction of 3.5 g of lactam **4a** with a stirred, refluxing solution of 3.5 g of $LiAlH_4$ in 290 ml of ether and 25 ml of THF for 3.5 hr, followed by treatment with water (17.5 ml, stirred 1 hr), filtration, and evaporation of the dried ($K_2CO_3$) solution, gave 2.1 g (63%) of amine as crystals from ether, mp *ca.* 95–100°. A sample, recrystallized from methanol and dried *in vacuo* at 75°, had mp 85–88°; ir 3.53 (weak) and 6.25 $\mu$; uv 254 nm ($\epsilon$ 6940), 271 (3790), and inflection at 286 (1950); nmr ($CDCl_3$) $\delta$ 7.4–6.8 (m, 8, ArH), 5.56 (s, 1, methine), 4.02 (s, 2, methylene position 9), and 3.6–2.6 (m, 4, methylenes) with 2.9 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.54; H, 7.07; N, 11.37.

The corresponding hydrochloride was recrystallized from ethanol–ether as colorless crystals: mp 180–183° dec; ir 4.57 $\mu$ (intense, broad); uv 251 nm ($\epsilon$ 6500), inflection at 270 (3150) and 276–290 (2040).

*Anal.* Calcd for $C_{17}H_{18}N_2 \cdot HCl$: C, 71.19; H, 6.68; N, 9.77. Found: C, 71.78; H, 6.69; N, 9.85.

**Compound 5b**, prepared by similar $LiAlH_4$ reduction of **4b**, crystallized in ether–ligroin and was recrystallized from methanol: crystals; mp 109–110.5°; ir 3.64 (weak) and 6.28 $\mu$; uv 262 nm ($\epsilon$ 9320) and inflections at 272 (7130), 300 (1970); nmr ($CDCl_3$) $\delta$ 7.4–6.8 (m, 7, ArH), 5.53 (s, 1, methine), 4.06 (s, 2, methylene at position 9), and 3.6–2.6 (m, 4, methylenes) with 2.9 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{17}ClN_2$: C, 71.69; H, 6.02; N, 9.84. Found: C, 71.49; H, 6.27; N, 9.90.

The corresponding hydrochloride, recrystallized from ethanol–ether, had mp 248–250° dec; ir 4.54 (intense, broad); uv 258 nm ($\epsilon$ 9270) and 298 (2100).

*Anal.* Calcd for $C_{17}H_{17}ClN_2 \cdot HCl$: C, 63.56; H, 5.65; N, 8.72. Found: C, 63.40; H, 5.81; N, 8.66.

**Compound 5c**, from similar reduction of **4c**, did not crystallize, and was characterized by preparation of the corresponding hydrochloride: slightly unstable and discolored crystals; mp 231–233° dec (from ethanol–ether); ir 4.36–4.44 $\mu$ (strong); uv 222 nm ($\epsilon$ 32,650), 252 (6520), and inflections at 270 (3520) and 288 (1930).

*Anal.* Calcd for $C_{18}H_{20}N_2O \cdot HCl$: C, 68.23; H, 6.68; N, 8.84. Found: C, 68.53, 68.06; H, 6.64; N, 8.74.

**Compound 5e**, from **4e**, in the course of isolation was converted with 10% hydrochloric acid to the corresponding, water-insoluble hydrochloride, which was recrystallized from ethanol (Norit) and a small amount of ether: slightly lavender crystals; mp 225–227°

dec; ir 4.42 μ (intense); uv 256 nm (ε 9960) and 297 (4070) with inflection at 269 (5430).

*Anal.* Calcd for $C_{25}H_{26}N_2O_2 \cdot HCl$: C, 70.99; H, 6.44; N, 6.62. Found: C, 71.31; H, 6.65; N, 6.59.

**6,7-Dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-9(5*H*,13b*H*)-one (6).**—To a solution of 3.6 g of **4d** in 200 ml of glacial acetic acid containing *ca.* 3 g of dry HCl was added 0.5 g of 10% Pd/C, and the suspension was shaken under 45 lb of $H_2$ at 50° for 6.5 hr. Evaporation of the filtered solution and trituration of the residue with ether gave 3.0 g of the hydrochloride as crystals (from ethanol): mp 253–256° dec; ir 3.79 (broad) and 5.84 μ; uv 240 nm (ε 11,950) and 279 (2950) with inflection at 227 (14,490).

*Anal.* Calcd for $C_{16}H_{14}N_2O \cdot HCl$: C, 67.01; H, 5.27; N, 9.77. Found: C, 67.22; H, 5.35; N, 9.42.

The corresponding base, from treatment of the hydrochloride in methanol with 10% NaOH solution, extraction with benzene, and recrystallization from ether–benzene, had mp 135–137°; ir 3.00 and 5.96 μ; uv 241 nm (ε 12,020) and 279 (3450) with inflection at 228 (14,630); nmr ($CDCl_3$) δ 8.0–6.7 (m, 9, ArH and NH), 5.72 (s, 1, methine), and 4.5–3.3 (m, 4, methylenes).

*Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.95; H, 6.04; N, 10.92.

**2,3-Dimethoxy-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine Hydrochloride.**—A solution of 1.3 g of **5e** in 200 ml of ethanol and 1 ml of 5% ethanolic HCl, containing 0.5 g of 10% Pd/C, was shaken under 45 lb of $H_2$ at 60° for 8 hr, cooled, and filtered, and the solvent was evaporated, The crude salt with dilute NaOH gave an oily base which, after ether–benzene extraction, drying ($K_2CO_3$), and evaporation, was reconverted to hydrochloride, 0.6 g of gray crystals, mp *ca.* 217° dec, purified by recrystallization from ethanol: colorless crystals: mp 244–246° dec (after drying *in vacuo* at 80°); ir 3.09 (moderate to intense, sharp), and 4.05–4.11 μ (intense); uv 210 nm (ε 47,100), 248 (10,540), 270 (2310), and 297 (5140).

*Anal.* Calcd for $C_{18}H_{20}N_2O_2 \cdot HCl$: C, 64.95; H, 6.36; N, 8.42. Found: C, 65.13; H, 6.50; N, 8.46.

**5,6-Dihydroisoindolo[1,2-*a*][2]benzazepin-9(7*H*,13b*H*)-one (8b).** **A.**—Crude 3-(γ-phenylpropylamino)phthalide (**7b**) was prepared by 1-hr reflux of a solution of 25 g of γ-phenylpropylamine and 26.8 g of phthalaldehydic acid in 250 ml of benzene under water separator, and evaporation of the solvent: viscous, semicrystalline oil, ir 5.71 μ.

**B.**—Cyclization of 30 g of crude A with 200 g of PPA at 95° for 1.5 hr, hydrolysis of the cooled, light brown solution with 1 l. of ice–water, and extraction with ether gave after evaporation of the washed and dried ether solution 8.5 g (30%) of crystals, mp 140–145° from ether, raised to 143–145° on recrystallization from ethanol: ir 5.91 μ; uv 249 nm (ε 5210) and inflections at 270 (3340) and 279 (1890); nmr ($CDCl_3$) δ 7.9 (q, 1, proton 10), 7.6–7.0 (m, 7, ArH), 5.74 (s, 1, methine), 4.38 (octet, 1, probably proton $7_{eq}$), 3.4 (m, 1, probably proton $7_{ax}$), 2.73 (m, 2, methylene position 5), and 2.4–1.7 (m, 2, methylene position 6).

*Anal.* Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.15; H, 6.17; N, 5.79.

**13b-Hydroxy-5,6-dihydroisoindolo[1,2-*a*][2]benzazepin-9(7*H*,13b*H*)-one (9b).**—A solution of 5.2 g of **8b** in 50 ml of THF was added (10 min) to $LiAlH_4$ (4 g) in 200 ml of THF with stirring, and the suspension was refluxed and stirred for 2 hr. There was initially a green color, later becoming orange-brown. The cooled mixture was diluted with ether, treated with 20 ml of water cautiously, stirred for 1 hr, and filtered. Evaporation of the dried ($K_2CO_3$), yellow filtrate gave *ca.* 4.5 g of crude crystals. Basic material (1.4 g of brown, unstable oil) was removed by extraction with dilute HCl, and the washed ($NaHCO_3$, $H_2O$) and dried ether solution of neutral material was evaporated, to give 3 g of crude crystals, mp *ca.* 200°, purified by tlc and recrystallization from ethanol to give colorless crystals: mp 230–233° dec; ir 3.19 and 5.97 μ; uv 256 nm (ε 3880) and inflection 265 (3360); nmr (DMSO) similar to that of **8b** in complexity, methine absent, and δ 6.9 (s, 1, exchanges with $D_2O$, OH).

*Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.07; H, 5.73; N, 4.95.

**Bis(2-benzoyl-4-chloroanilino)methane (11).**—A solution of 15 g of 2-amino-5-chlorobenzophenone in 125 ml of glacial HOAc was treated with 6.3 g of paraformaldehyde and warmed on a steam cone for 1 hr. The cooled suspension of yellow crystals was filtered, and, after washing with water and drying, the crude product was recrystallized from ethyl acetate as yellow crystals: mp 184.5–186°; ir 3.05 (weak), 6.13, and 6.34 μ; uv 236 nm (ε 27,250) and 387 (6210); nmr ($CDCl_3$) δ 8.8 (t, 2, slow $D_2O$ exchange, NH), 7.6–6.7 (m, 16, ArH), and 4.77 (t, 2, $J$ = 6 Hz, methylene); mass spectrum $m/e$ 231 and 243.

*Anal.* Calcd for $C_{27}H_{20}Cl_2N_2O_2$: C, 68.22; H, 4.24; N, 5.89. Found: C, 68.43; H, 4.12; N, 5.79.

The compound is readily distinguished from **12a** by spectra and the fact that with 18% aqueous HCl it does not develop a red color.

Compound **11** was also obtained by (a) treatment of **12a** (2.9 g) with warm, ethanolic $NH_3$ (700 ml) for several hours, (b) treatment of **12a** with aqueous, ethanolic NaOH solution, and (c) by treating **12a** with a warm buffered aqueous, alcoholic solution of hydroxylamine.

**2-*N*-(Cyanomethyl)amino-5-chlorobenzophenone (12a).**—A dry mixture of 14.6 g (0.063 mol) of 2-amino-5-chlorobenzophenone, 5.9 g (0.196 mol) of paraformaldehyde, and 12.4 g (0.191 mol) of KCN was treated with 110 ml of glacial HOAc, and the suspension was stirred for 1 hr. There was a spontaneous temperature rise to 41° at first, and later formation of a thick suspension of yellow solid. The suspension was treated with 1700 ml of water and stirred for 0.8 hr, and the crude material was collected and washed with a number of portions of water. After air drying the crude, voluminous product (18 g, mp *ca.* 168–175°) was triturated with sufficient dry ether to provide a filterable suspension, and collected to give 16.0 g (94%) of yellow crystals: mp 177–180°, raised to 182–183° on further recrystallization from ether; ir 2.99 (moderate to weak) and 6.14 μ; uv 234 nm (ε 32,930), 382 (7070), and inflection at 256; nmr ($CDCl_3$) δ 8.5 (t, 1, slow $D_2O$ exchange, NH), 7.7–6.7 (m, 8, ArH), and 4.2 (d, 2, $J$ = 6.5 Hz, methylene).

*Anal.* Calcd for $C_{15}H_{11}ClN_2O$: C, 66.54; H, 4.10; N, 10.35. Found: C, 66.52; H, 4.04; N, 10.24, 10.52.

The compound developed a bright red color when treated with 18% hydrochloric acid, but did not readily dissolve. The same product, together with 2-acetylamino-5-chlorobenzophenone (colorless, mp 117–119°), was obtained when 12 g of **11** and 2 g of KCN in 50 ml of acetic anhydride and 100 ml of glacial HOAc were heated for 2 hr on a steam cone; evaporation to *ca.* 75 ml volume gave crystals which were collected, washed with water, and recrystallized from ether as yellow crystals, mp 179–180°, having the same spectra as the first sample of **12**.

The carbinol corresponding to **12a**, 2-(α-hydroxybenzyl)-4-chloroanilinoacetonitrile, was prepared by reduction of **12a** with excess $NaBH_4$ in methanol (heated for 0.5 hr), isolated by treatment with water and extraction with ether, and recrystallized from ether–ligroin as colorless crystals: mp 140–142°; gradual decomposition to a gum on standing; ir 2.93–2.97, 4.43, and 6.20–6.29 μ; uv 249 nm (ε 14,570) and 300 (2810); nmr ($CDCl_3$) δ 7.5–6.6 (m, 8, ArH), 5.82 (s, 1, methine), 5.3 (t, 1, very broad, rapid $D_2O$ exchange, NH), 4.02 (d, 2, $J$ = 6.5 Hz, methylene), and 2.7 (s, 1, $D_2O$ exchange, OH).

*Anal.* Calcd for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80; N, 10.27. Found: C, 65.70; H, 5.07; N, 10.36.

**α-(2-Benzoyl-4-chloroanilino)acetamide (12b).**—To a solution prepared by adding 6 g of paraformaldehyde to 11 g of KCN in 80 ml of water was added 21 g of 2-amino-5-chlorobenzophenone and enough ethanol (*ca.* 300 ml) to dissolve the material. The solution was refluxed gently on a steam cone for 0.5 hr, then evaporated on a steam cone for 1 hr to a volume of 200 ml. After dilution with water, the yellow oil was extracted with ether. The ether solution was washed with three portions of water, dried ($MgSO_4$), and evaporated to a smaller volume. The crystals which separated were collected and washed with ether: 1.2 g of bright yellow needles; mp 222–225°, raised to 226–228° on recrystallization from ethyl acetate or ethanol; ir 2.90, 3.04, 3.15, 5.96, and 6.13 μ; uv 233 nm (ε 27,150), inflection at 272, and 395 (6420); nmr (DMSO) δ 8.63 (t, 1, slow $D_2O$ exchange, NH), 7.7–6.6 (m, 10, 2 slow $D_2O$ exchanges, ArH and $CONH_2$), 3.86 (d, 2, $J$ = 5 Hz, methylene).

*Anal.* Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; N, 9.70. Found: C, 62.13; H, 4.83; N, 9.70.

The same product, again in low yield (0.6 g), was obtained when 5 g of bisanilinomethane (**11**) was heated (100°) with aqueous alcoholic KCN solution for 10 hr.

**Ester 12c.**—Nitrile **12a** was refluxed for 1 hr with 50–100 parts of saturated, methanolic HCl, and the neutral product was isolated as usual, after distillation *in vacuo* of most of the excess reagent, as an oil: ir 5.73 and 6.12–6.14 μ; uv 235 nm (ε 29,880), inflections at 260, 272, and 390 (7100).

**Ester 12d** was prepared similarly using ethanol, as crystals, mp 103–106° (lit.[3] mp 104–106°).

**1,2-Dihydro-4-phenyl-6-chloroquinazoline 3-Oxide (13).**[17]—A solution of 1.6 g of $NaHSO_3$ in 20 ml of water was combined with 2.1 ml of 36% formalin, 1.4 g of β-oxime **10c** and 15 ml of DMF were added, and the solution was heated on a steam cone for 0.5 hr and let stand overnight. A solution of KCN (3.8 g in 20 ml of water) was added and heating was resumed for 10 min, resulting in separation of yellow needles which were collected, washed with water, and dried, yield 1.1 g, mp 179–182°. Trituration with a small amount of methanol raised the melting point to 183–187°. A pure sample, recrystallizing from ethyl acetate as cottony, yellow needles, had mp 185–187°; ir 3.13 (moderate), 6.20, and 6.67 μ; uv 234 nm (ε 21,000), 248 (19,000), and 382 (3300) with inflection at 305 (7000); nmr ($CDCl_3$) δ 7.7–6.63 (m, 8, ArH) and 5.04 (s, 2, methylene); NH discerned only on $D_2O$ exchange.

*Anal.* Calcd for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 64.81; H, 4.31; N, 10.81.

The experiment was repeated, omitting the KCN treatment, to give on dilution with water the same compound **13**.

The same compound was isolated, in lower yield, from (a) treatment of **14** with aqueous, methanolic KCN, (b) from reaction of **12a** with a neutral, aqueous, alcoholic solution of hydroxylamine at room temperature, and (c) from mixtures of α- and β-oximes **10b,c** with HCHO under various conditions.

The dihydroquinazoline oxide was $FeCl_3$ negative, and gave with HCl a bright red, unstable, sparingly water-soluble hydrochloride.

A sample of 6-chloro-1,2-dihydro-2,2-dimethylquinazoline 3-oxide,[18] prepared for comparison with **13** by allowing a solution of oxime **10c** in acetone to stand at room temperature for 9 days, consisted of yellow crystals: mp 234–236°; ir 3.09 (moderate) and 6.26 μ (moderate to weak); uv 234 nm (ε 23,140), inflection at 252 (20,610), 294–304 (7390), and 390 (3940); nmr (DMSO) δ 7.7–6.4 (m, 9, 1 $D_2O$ exchange, ArH and NH) and 1.55 (s, 6, $CH_3$).

**7-Chloro-1,2-dihydro-5-phenyl-3,1,4-benzoxadiazepine (14).**—A solution of 8 g of oxime **10b** (containing a small amount of **10c**) and 1.2 g of paraformaldehyde in 110 ml of ethanol and 1 ml of HOAc was refluxed on a steam cone for 5.5 hr. Evaporation of the alcohol gave a green-orange syrup which crystallized on standing with dry ether. The crude, yellowish crystals were collected and triturated with methanol, which removed most of the yellow by-product, giving 5.2 g of finely divided crystals, mp 180–182° dec. Recrystallization from acetone afforded a pure sample of **14** as colorless crystals: mp 181–182° dec; ir 2.92 (moderate) and 6.25 μ (weak, sharp); uv 250 nm (ε 22,250), 304 (5220), and 376 nm (1410); nmr (DMSO) δ 7.6–6.7 (m, 8–9, ArH and NH) and *ca.* 5.1 (2, methylene).

*Anal.* Calcd for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 65.05; H, 4.35; N, 10.85.

From the methanol filtrate of the foregoing purification on evaporation there was obtained a small sample of **13**, yellow crystals, mp 175–178°, spectra the same as those of the preceding sample of that compound.

Compound **14** was $FeCl_3$ negative. In the presence of 10–15% hydrochloric acid it gradually became red and eventually was hydrolyzed back to oxime **10b**.

**4-Phenyl-6-chloroquinazoline (16).**—A sample (0.5 g) of **13** in acetic anhydride (15 ml) was heated for 0.5 hr on a steam cone and the solution was evaporated. The residue crystallized with the aid of ether to give a quantitative yield of **16** as colorless needles: mp 139–140°; ir 6.25 (weak) and 6.43–6.51 μ; uv 229 nm (ε 42,740), 272 (7830), and 326 (6400).

*Anal.* Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.84; H, 3.85; N, 11.53.

**Preparation of 16. A. Leuckart Reaction.**—A solution of 20 g of **10a** and 30 g of $HCOONH_4$ in 100 ml of $HCONH_2$ and 75 ml of HCOOH (97–100%) was distilled (1 hr) until the vapor temperature reached 175°, then refluxed for 5 hr, cooled, and poured into 300 ml of ice–water. The crystals of the 6-chloro-3,4-dihydro-4-phenylquinazoline formic acid salt (28 g) were collected, washed with water, and dried, mp 139–141° (from EtOAc).

*Anal.* Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.50; N, 9.70. Found: C, 62.18; H, 4.66; N, 9.54.

Treatment of the salt with dilute NaOH solution gave 6-chloro-3,4-dihydro-4-phenylquinazoline (**20**) as crystals from aqueous methanol: mp 176–178° (lit.[20,22] mp 173–174°); ir 3.18 (moderate), 6.23, 6.29, and 6.47 μ; uv 226 nm (ε 17,250) and 294 (8300).

**B. Aromatization.**—Solution of 11.2 g of **20** from A in 1 l. of cymene containing 5 g of 10% Pd/C catalyst was boiled for 10 min to remove water and refluxed for 1.5 hr. The hot suspension was filtered, the filtrate was evaporated, and the crude product (4.7 g) was recrystallized from methanol to give **16** as very pale yellow needles, mp 138.5–139°, mixture melting point with **16** prepared from **13** undepressed and spectra identical.

Compound **16** can also be prepared from the corresponding 2-chloro derivative.[21]

**2-*N*-(Cyanomethyl)amino-5-chlorobenzophenone Oxime (18a).**—Formaldehyde bisulfite solution was prepared from 23.4 g (0.225 mol) of $NaHSO_3$ in 45 ml of water and 20 ml (0.26 mol) of 36% formalin, α-oxime **10b** (23.4 g, 0.096 mol) and DMF (115 ml) were added, and the mixture was heated on a steam cone with stirring for 0.8–1 hr to give a somewhat turbid, yellow solution. On standing overnight at room temperature, the solution deposited only a small amount of insoluble material. The anilinomethanesulfonate solution was treated with a solution of 17.5 g (0.27 mol) of KCN in 90 ml of water and warmed gently on a steam cone with swirling for 0.7 hr. The cooled suspension was filtered to remove precipitated, water-soluble salts (34 g), and the rather dark filtrate was diluted with *ca.* 1.5 l. of water. The crude product was extracted with ether; the ether solution was washed with five portions of water, dried ($MgSO_4$), and evaporated without heating the residue above *ca.* 60°. Trituration with ether afforded two crops of crystalline **18a** totaling 10.5 g (39%), mp 174–177°. A sample recrystallized from methanol had mp 179.5–181° (decomposition follows on further heating); the mixture melting point with **10b** (mp 177–179°) was 150–155° (depressed); ir 3.01–3.02 (intense), 4.42 (weak, sharp), and 6.27–6.34 μ (moderate to weak); uv 245 nm (ε 24,940), 292 (2210), and 309 (2480); nmr (DMSO) δ 11.6 (s, 1, $D_2O$ exchange, NOH), 7.6–6.8 (m, 8, ArH), 5.36 (t, 1, $D_2O$ exchange, NH), and 4.22 (d, 2, $J$ = 6.5 Hz, methylene).

*Anal.* Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.94; H, 4.43; N, 14.70.

A difficultly separated mixture of **18a** and **13** was formed when crude oximes **10b,c**, was subjected to the same sequence of reactions.

**Ester 18b.**—Exposure of samples of **18a** to methanolic HCl under various conditions produced a yellow color and resulted in rapid formation of $NH_4Cl$. Upon addition of ether and isolation of neutral product by evaporation of the washed ($NaHCO_3$ solution, water) and dried ($MgSO_4$) solution, there were obtained nearly quantitative yields of colorless crystals (from ether): mp 129–132°; ir 2.95, 3.11 (broad), and 5.70 μ; uv 249 nm (ε 24,270) and 316 (2280).

*Anal.* Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.57; H, 4.71; N, 8.66.

**Ester 18c.**—A solution of 2 g of **18a** in saturated ethanolic HCl (55 ml) was allowed to stand overnight. Dilution with ether, isolation of the neutral product as usual (2 g), and recrystallization from ether gave colorless crystals: mp 138.5–140° (lit.[3] mp 132–134°); ir 2.96, 3.13 (broad), and 5.76 μ; uv 249 nm (ε 24,310) and 316 (2400); nmr ($CDCl_3$) δ 9.1 (s, 1, $D_2O$ exchange, =NOH), 7.6–6.5 (m, 8, ArH), 4.67 (t, 1, $D_2O$ exchange, NH), 4.18 (q, 2, $J$ = 7 Hz, ester $CH_2$), 3.89 (d, 2, $J$ = 6 Hz, *N*-methylene), and 1.22 (t, 3, $CH_3$).

*Anal.* Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.35; H, 5.15; N, 8.42. Found: C, 61.49; H, 5.35; N, 8.30.

Hydrogenation of **18a** in ethanolic $NH_3$ in the presence of Ni gave amine **18d** as crystals from ether: mp 125–130°; ir 3.01 (strong) and 6.29–6.35 μ; uv 250 nm (ε 24,380), 320 (2290), and inflection 292 (2000); nmr δ *ca.* 11 (=NOH signal, $D_2O$ exchange).

*Anal.* Calcd for $C_{15}H_{16}ClN_3O$: C, 62.17; H, 5.57; N, 14.50. Found: C, 61.81; H, 5.65; N, 14.00.

Compound **17** (*O,N*-diacetyl derivative of **10b**) was obtained when samples of **10b** or **14** were heated at 100° with excess acetic anhydride for 0.5 hr. Evaporation of excess reagent and recrystallization from ether gave colorless crystals: mp 175–176°; ir 3.00, 5.66, and 5.90 μ; uv inflection 242 nm (ε 19,280); nmr ($CDCl_3$) δ 8.3–7.0 (m, 9, ArH and $D_2O$ exchange NH), 2.10 (s, 3, $CH_3$ of *O*-acetyl), and 1.98 (s, 3, $CH_3$ of *N*-acetyl).

*Anal.* Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.73; H, 4.80; N, 8.36.

**Compound 19.**—A sample (1 g) of **18a** was similarly heated with $Ac_2O$ (30 ml) on a steam cone for 0.5 hr, the reagent was evaporated, and the readily crystallizing residue was triturated with ether and recrystallized from methanol as colorless crystals:

mp 208–210°; ir 3.00 and 5.69 μ; uv 249 nm (ε 27,980) and inflection at 308 (1900); nmr ($CDCl_3$) δ 7.7–6.7 (m, 8, ArH), 5.14 (t, 1, $D_2O$ exchange, NH), 4.13 (d, 2, $J$ = 6.5 Hz, methylene), and 2.07 (s, 3, acetyl).

*Anal.* Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.40; H, 4.42; N, 12.72.

**2-(*N*-Acetyl-*N*-methylamino)-5-chlorobenzophenone (21b).**—To 6.0 g of 56% NaH in 100 ml of DMF was added 29.3 g of **21a**[14] (prepared by warming **10a** with excess $Ac_2O$ on a steam cone for 2 hr, evaporating, and triturating the residue with ether; mp 115°) with cooling (20°), and the mixture was stirred for 10 min; iodomethane (110 ml) was added while the exothermic reaction was controlled (to 70°) over the course of 10 min. The mixture was warmed on a steam cone for 15 min while excess reagent was evaporated, and the mixture was cooled and poured into water. Extraction with ether, evaporation of the washed (water) and dried ($MgSO_4$) ether solution, and trituration with a small amount of ether gave 24 g of crystals: mp 65–71°, raised to 71–73.5° on recrystallization; ir 6.00 μ; uv 246 nm (ε 14,840).

*Anal.* Calcd for $C_{16}H_{14}ClNO_2$: C, 66.78; H, 4.90; N, 4.87. Found: C, 67.00; H, 4.85; N, 4.86.

**6-Chloro-1-methyl-4-phenyl-2-quinolone (22).**[49]—A solution prepared by combining 12 g of **21b** in 60 ml of ethanol and 10.5 g of NaOH in 30 ml of water was refluxed for 4.5 hr. Evaporation of the ethanol and treatment with water gave yellow crystals which were collected, washed with water, dried (yield quantitative), and recrystallized from ethanol as yellow needles: mp 145–147°; ir 6.07 μ; uv 237 nm (ε 50,370), 281 (6330), and 342 nm (ε 5980) with inflections at 212, 328, and 352 nm; nmr ($CDCl_3$) δ 7.7–7.3 (m, 8, ArH), 6.72 (s, **1**, methine), and 3.75 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; N, 5.19. Found: C, 71.29; H, 4.46; N, 4.88.

**2-*N*-Methylamino-5-chlorobenzophenone (23).**—A solution of 41.5 g of **21b** in 400 ml each of concentrated HCl and glacial HOAc was refluxed for 3 hr and distilled *in vacuo* to remove most of the excess reagents, the residue was treated with water, and the crystalline product was isolated by ether extraction, washing ($NaHCO_3$, $H_2O$), drying ($K_2CO_3$), and evaporating the ether: 36.1 g; mp (from EtOH) 94–95° (lit.[50] mp 94–96°); ir 3.02 and 6.18 μ; uv 235 nm (ε 25,390) and 395 (6900).

*Anal.* Calcd for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.92; N, 5.70. Found: C, 68.71; H, 4.79; N, 5.86.

**2-*N*-(Cyanomethyl)-*N*-methylamino-5-chlorobenzophenone (24).**—A dry mixture of 19.2 g of **23**, 7.0 g of paraformaldehyde, and 15.2 g of KCN was treated with 200 ml of glacial HOAc, and the suspension was magnetically stirred for 4.5 hr. Dilution with 1.5 l. of water, extraction with ether, and evaporation of the washed ($NaHCO_3$ solution, water) and dried ether solution gave 23.4 g of yellow oil, which crystallized on standing: 89% product by gpc; crystals from MeOH; mp 78–80°; ir 6.01 μ; uv 249 nm (ε 21,640); nmr ($CDCl_3$) δ 7.9–7.3 (m, 8, ArH), 3.84 (s, 2, methylene), and 2.75 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.46; H, 4.90; N, 9.84.

Amide corresponding to **24** was obtained on heating a sample of **24** with PPA for 0.5 hr. After treatment with water, the ether-extracted product crystallized on standing as yellow crystals (from ether): mp 110–112°; ir 2.94, 3.13, 5.89, and 6.10 μ; uv 251 nm (ε 23,030) and inflection at 380 (1390); nmr ($CDCl_3$) δ 8.1–7.1 (m, 9, 1 slowly $D_2O$ exchanges NH of $CONH_2$), 5.94 (s, very broad, 1, slowly $D_2O$ exchanges NH of $CONH_2$), 3.78 (s, 2, methylene), and 2.72 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.73; H, 5.02; N, 9.11.

**7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (25).**—A solution of 12 g of **24** in 200 ml of $NH_3$-saturated ethanol containing *ca.* 20 g of washed Ni catalyst (Grace 28) was shaken under 50 lb of $H_2$ for 6.5 hr. The filtered solution was evaporated. A solution of the crude residue in dilute HCl was filtered, washed with ether, and made basic by adding NaOH solution, and the base was isolated by extraction with ether and evaporation of the water-washed and dried ($K_2CO_3$) ether solution to give 8.5 g (75%) of orange oil, crystallizing on standing. Recrystallization from ether or aqueous ethanol afforded slightly orange or colorless crystals: mp 101–103° (lit.[31,32] mp 95–97°, 97–99°); ir 5.93 (weak), 6.20 μ; uv 229 nm (ε 21,810) and 358 (1870) with inflection at 248 (19190); nmr ($CDCl_3$) δ 7.75–6.8 (m, 8, ArH), 3.67 (m, 4, $CH_2CH_2$), and 2.77 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58; N, 10.35. Found: C, 71.09; H, 5.52; N, 10.13.

The corresponding hydrochloride was precipitated from ether with ethanolic HCl and recrystallized from ethanol–ether as yellow crystals: mp 257–258° dec; ir 3.79, 5.52, and 6.12 μ; uv 250 nm (ε 21,410) and 455 (4950).

*Anal.* Calcd for $C_{16}H_{15}ClN_2 \cdot HCl$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.83; H, 5.36; N, 9.06.

The sparingly water-soluble hydrochloride of *N*-(2-aminoethyl)-*N*-methyl-2-benzoyl-4-chloroaniline was obtained from **25** with hydrochloric acid as colorless crystals from water: mp 258–261° dec; ir 2.92, 6.23 μ; uv 236 nm (ε 37,520) and 262 (9890) with inflections at 230 (36,920) and 300 (7160).

*Anal.* Calcd for $C_{16}H_{17}ClN_2O \cdot HCl$: C, 59.08; H, 5.58; N, 8.62. Found: C, 59.74; H, 5.32; N, 8.81.

**5-Chloro-1-methyl-3-phenylindole-3-carbonitrile (26a).**—Nitrile **24** (5.1 g) was added to a solution of Na (0.45 g) in methanol (50 ml) and the solution was refluxed for 0.2 hr. The suspension of crystals was cooled and the product was collected and washed with methanol: yield 4.4 g (92%) of colorless crystals; mp 132–133°, raised to 134–135° (lit.[34] mp 131°) on recrystallization from methanol; ir 4.50 (moderate to intense, sharp) and 6.24 μ (weak, sharp); uv 238 nm (ε 42,000), 301 (13,500), and 327 (8800); nmr ($CDCl_3$) δ 7.9–7.3 (m, 8, ArH) and 3.92 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.04; H, 4.16; N, 10.51. Found: C, 72.17; H, 4.36; N, 10.52.

The same indole **26a** was obtained when **24** was allowed to stand with (a) dry HCl in ether or (b) a solution of $MeNH_2$ in MeOH. Compound **26a** resisted reaction with (a) refluxing methanolic HCl, (b) PPA at 100°, and (c) refluxing, concentrated HCl–glacial acetic acid.

**Amidoxime 26b.**—A solution of hydroxylamine was prepared from 2.73 g of Na in 300 ml of ethanol and 8.2 g of $H_2NOH \cdot HCl$, nitrile **26a** (4.2 g) was added, and the whole was refluxed for 6 hr. The filtered solution was evaporated, and a twice filtered and concentrated, dry ether solution of the material was gassed gently with dry HCl to give 3.5 g (66%) of the hydrochloride as cream-colored crystals: mp 191–193° dec, raised to 195–197° on recrystallization from ethanol–ether; ir 2.95, 3.05–3.18 (bonded), 5.99–6.03 (doublet), and 6.23 μ; uv 227 nm (ε 35,680) and 298 (9660) with inflections at 212 (29,760) and 232 (35,110).

*Anal.* Calcd for $C_{16}H_{14}ClN_3O \cdot HCl$: C, 57.15; H, 4.50; N, 12.50. Found: C, 57.27; H, 4.59; N, 12.51.

Compound **26b** was also prepared directly from **24** (2.9 g) by similar reaction (4 hr reflux) with ethanolic hydroxylamine (from 3.5 g of $H_2NOH \cdot HCl$ and 1.15 g of Na), and isolated as the hydrochloride (1.5 g), mp 192–193° (from ethanol–ether), spectra identical with those of the above sample.

**Amide 26d.**—The preceding experiment was repeated with 3 g of **26a**, and, after concentration of the filtered ethanol solution, water was added to the crude, residual base, resulting in partial hydrolysis. Together with 2.1 g of ether-soluble, crude amidoxime **26b** ($FeCl_3$, green test) there was isolated 1.1 g of ether-insoluble, colorless crystals of **26d** ($FeCl_3$, test negative): mp 185–190°, raised to 193–194° on recrystallization from ethanol (lit.[34] mp 192°); ir 2.92, 3.04, 3.16, and 6.04 μ.

**Amine 26c.**—Hydrogenation of either **26a** or **26b** in ethanol with Ni catalyst was carried out as described in preparation of **25**. The crude amine was converted to the corresponding hydrochloride, recrystallizing from ethanol–ether as colorless crystals: mp 260–262° dec (lit.[34] mp 256° dec); ir broad NH bands; uv 236 nm (ε 36,000) and 263 (9800) with inflections at 235 (36,000), 284 (8500), and 300 (7100); nmr (DMSO) δ 8.92 (broad s, 3, $D_2O$ exchange, $NH_2 \cdot HCl$), 7.8–7.2 (m, 8, ArH), 4.25 (s, 2, methylene), and 3.94 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{15}ClN_2 \cdot HCl$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.39; H, 5.45; N, 8.82.

**5-Methyl-6,11-morphanthridinedione (28b).**—A mixture of 33 g of **28a**[35,37] and 150 ml of DMSO was treated with 17 g of potassium *tert*-butoxide and stirred for 10 min; to the resulting solution was added 60 ml of $CH_3I$, and the reaction was allowed to proceed exothermically. The intense green-brown color was discharged. After 15 min the solution was warmed briefly to *ca.* 80° and allowed to stand for 1 hr while cooling gradually to room temperature. Water (1 l.) was added, the oil was extracted with ether,

(49) T. Ishiwaka, M. Yonemoto, K. Isegawa, and Y. Fushizaki, *Bull. Chem. Soc. Jap.*, **43**, 1839 (1970).

(50) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

and the ether solution was washed with two portions of water, dried ($MgSO_4$), and evaporated, yield 26 g (74%) of crude crystals, mp 80–84°, suitable for further work. A pure sample, recrystallized from ether or methanol, had mp 98–99°; ir 6.01, 6.14, and 6.25 μ; uv 228 nm (ε 27,800) and inflections at 244 (20,580), 272 (7550), and 324 (1520).

*Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.25; H, 4.83; N, 6.01.

**2-Chloro-5-methyl-6,11-morphanthridinedione (28c)** was obtained by similar methylation of 2-chloro-6,11-morphanthridinedione[35] in 79% yield as colorless crystals from ethanol: mp 154–155° (lit.[11,35] mp 148–151°); ir 5.98 and 6.10 μ; uv 225 nm (ε 26,000) and 331 (1200) with inflections at 240–245 (20,000) and 280–290 (1800).

*Anal.* Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.79; N, 5.13. Found: C, 66.30; H, 3.71; N, 5.16.

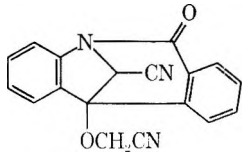
**Compound 28d** was obtained by similar alkylation of **28a** with benzyl chloride in 78% yield as colorless crystals from ethanol: mp 106–107°; ir 5.95, 6.08, and 6.27 μ; uv inflections at 224 nm (ε 27,960), 274 (7230), and 318 (1720).

*Anal.* Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.20; H, 4.94; N, 4.20.

**Compound 28e.**—Morphanthridinedione **28a** (18.8 g) in 90 ml of DMSO was treated with potassium *tert*-butoxide (10.0 g), the suspension was swirled until the materials dissolved, and 7 ml of chloroacetonitrile was added. A strongly exothermic reaction ensued and the intense green color was discharged. After *ca.* 15 min, the solution was reheated to 80° briefly and allowed to stand for 1 hr and cool slowly to room temperature. After addition of water (1 l.) the crude, neutral product was isolated by extraction with ether as for **28b**. The concentrated ether solution was filtered to remove insoluble material and evaporated. The slowly crystallizing residue on trituration with methanol gave 7.2 g (33%) of crystals, mp *ca.* 150°. Recrystallization from methanol afforded material: mp 171–173° after drying *in vacuo;* ir 6.02, 6.11, and 6.28 μ and a barely visible CN signal at *ca.* 4.47 μ; uv 221 nm (ε 30,000) and 274 (6320); nmr ($CDCl_3$) δ 7.8–7.2 (m, 8, ArH) and 4.8 (s, 2, methylene).

*Anal.* Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.45; H, 3.92; N, 10.63.

When this reaction was conducted in essentially the same way, using 15.6 g of **28a**, 8 g of potassium *tert*-butoxide, and 14 ml of $ClCH_2CN$, the isolated, crude material contained 2.9 g of recovered **28a** (mp 250°), 6.5 g of **28e**, and 0.5 g of material, mp *ca.* 215–216°, which was sparingly soluble in alcohols. A pure sample of the latter material (recrystallized from ethanol) had mp 225–226°. Analysis and spectra indicated that its structure was i: ir 4.46 (very weak), 6.09, and 6.26 μ; uv 269–274 nm




i

(ε 3180) with strong end absorption; nmr (DMSO) δ 8.1–7.3 (m, 8, ArH), 5.15 (q, 2, $J_{AB}$ = 17 Hz, methylene), and 4.72 (s, 1, methine).

*Anal.* Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.55; H, 4.10; N, 13.78.

The structure of this compound was confirmed by independent synthesis of an identical sample, mp 227–229° (low yield), by treatment of **28e** with $ClCH_2CN$ and potassium *tert*-butoxide in THF (15-min reflux). In this reaction there was also formed regenerated **28a**, mp 249–251°, identical with authentic sample.

**Methyl *o*-2-Aminobenzoylbenzoate (29a, R′ = $CH_3$). A. Hydrolysis.**—Hydrolysis of 68 g of **28a** in 100 ml of methanol with 300 ml of 10% aqueous NaOH by warming for 0.8 hr on a steam cone gave a solution which was diluted with 400 ml of water, chilled, and slowly acidified with 18% HCl. The crystals were collected, washed with water, and air dried, to give 73.8 g of bright yellow *o*-2-aminobenzoylbenzoic acid, mp 190–200° (effervescing and resolidifying to give **28a**), as described in the literature.[40]

**B. Esterification.**—A solution of 73.5 g of acid from A in 3 l. of dry methanol was saturated with dry HCl and allowed to stand for 6 days. Most of the methanol was removed by distillation *in vacuo* on a stream cone. To the cooled residue ether was added, then water and $NaHCO_3$ solution to neutralize, and the ether extract, after washing with water and drying ($MgSO_4$), was evaporated to yield 56.5 g (73%) of yellow crystals: mp 113–117°, raised to 115–117° on recrystallization from ether; ir 2.92, 3.02, 5.84, and 6.10 μ; uv 227 nm (ε 26,900) and 372 (6400) with inflections at 256 (9120) and 280 (1990); nmr ($CDCl_3$) δ 8.2–6.1 (m, 10, 2 $D_2O$ exchange, ArH and $NH_2$) and 3.68 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.57; H, 5.11; N, 5.49.

**Acid 29b (R′ = H)** was prepared from **28b** by procedure A of the preceding experiment in quantitative yield as yellow crystals from methanol: mp 207–208° dec; ir 3.00 (moderate), 3.84–4.31 (moderate to weak), 5.82, and 6.19 μ; uv 210 nm (ε 27,340), 226 (27,000), 261 (8300), and 390 (7600); nmr (DMSO) δ 13–12 (broad s, 1, $D_2O$ exchange, COOH), 9.0–6.3 (m, 9, 1 $D_2O$ exchange, ArH and NH), and 2.9 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.70; H, 5.36; N, 5.52.

The *N*-chloroacetyl derivative of **29b** (R′ = H), from **29b** (R′ = H) with chloroacetyl chloride, after recrystallization from ether had mp 173–175°; ir 5.83, 6.00 and 6.13 μ; uv inflection at 285 nm (ε 3380).

*Anal.* Calcd for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22. Found: C, 61.65; H, 4.25; N, 4.43.

**Acid 29c (R′ = H).**—Similar ring opening of 46 g of **28c** in 500 ml of methanol with 250 ml of 10% NaOH solution (2 hr heating on steam cone) and careful HCl acidification of the cooled, diluted solution gave 48 g (97%) of yellow crystals: mp 215–218° dec, raised to 221–223° dec on recrystallization from ethanol; ir 2.98, 3.85, 5.80, and 6.19 (6.27) μ; uv 228 nm (ε 30,550), 263 (8610), and 400 (7420); nmr (DMSO) δ 13–12 (broad s, 1, $D_2O$ exchange, COOH), 8.8–6.7 (m, 8, 1 $D_2O$ exchange, ArH and NH), and 2.94 (d, 3, $NCH_3$).

*Anal.* Calcd for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; N, 4.84. Found: C, 61.87; H, 4.46; N, 4.79.

**Acid 29d (R′ = H)** was obtained from similar hydrolytic ring opening of **28d** as yellow crystals from ether: mp 162–164° dec; ir 3.01 (moderate), 3.78–3.95 (weak), 5.92, and 6.14 μ; uv 229 nm (ε 28,430), 261 (9540), and 386 (8000).

*Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.00; H, 5.32; N, 4.10.

**Acid 29e (R′ = H).**—Potassium *tert*-butoxide powder (1 g) was exposed to atmospheric moisture for 1 hr and added to a solution of 2 g of **28e** in 50 ml of THF. The deep reddish-brown mixture was heated on a steam cone for 15 min. The THF was evaporated, the residue was taken up in water and acidified with dilute HCl, and the yellow-brown precipitate was extracted with ether. The washed and dried ether solution, after being evaporated to small volume, gave several small crops of brownish-yellow crystals, mp *ca.* 190–197° dec. Further recrystallization from ether afforded yellow crystals: mp 203–205° dec; ir 2.98, 5.92, and 6.12 μ; uv 225 nm (ε 26,430), 257 (8700), and 365 (6430) with inflection at 282; nmr (DMSO) δ 13–12 (broad, 1, $D_2O$ exchange, COOH), 8.8 (t, 1, $J$ = 6.5 Hz, $D_2O$ exchange, NH), 8.1–6.4 (m, 8, ArH), and 4.6 (d, 2, $J$ = 6.5 Hz, collapse to s on $D_2O$ exchange of NH, methylene).

*Anal.* Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.62; H, 4.64; N, 9.69.

**Ester 29e (R′ = $CH_3$).**—After 1.5 g of **28e** was treated with 0.7 g of potassium *tert*-butoxide in 100 ml of THF and warming for 10 min, iodomethane (10 ml) was added and the solution was refluxed for 1 hr. The evaporated (*in vacuo*) suspension was treated with water, and the product was extracted with ether and isolated as usual to give 0.75 g of pale yellow crystals (mp *ca.* 130°), purified by recrystallization from methanol: mp 142–143°; ir 3.01, 5.80, and 6.10 μ with barely discernible CN peak at *ca.* 4.46 μ; uv 226 nm (ε 26,030), 257 (8980), and 367 (6550), with inflections at 282 (1910); nmr ($CDCl_3$) δ 8.98 (t, 1, $J$ = 6.6 Hz, $D_2O$ exchange, NH), 8.2–6.5 (m, 8, ArH), 4.26 (d, 2, $J$ = 6.6 Hz, collapse to s on $D_2O$ exchange of NH, methylene), and 3.67 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.53; H, 4.79; N, 9.54.

**Ester 29b (R′ = $CH_3$)** was prepared by esterification of **29b** (R′ = H) (18 g) with 2 l. of methanolic HCl (let stand 5 days) following procedure B as for **29a** (R′ = $CH_3$): yield 17.3 g of yellow crystals from methanol; mp 87–89°; ir 3.01, 5.80, and 6.15 μ; uv 224 nm (ε 29,950), 251–263 (8180), and 391 (8290)

nmr ($CDCl_3$) δ 8.75 (s, 1, broad, $D_2O$ exchange, NH), 8.2–6.3 (m, 8, ArH), 3.7 (s, 3, ester $CH_3$), and 2.98 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.18; H, 5.58; N, 4.96.

**Ester 29c (R′ = $CH_3$)** was prepared from **29c** (R′ = H) by the same procedure, in 95% yield as yellow crystals (from MeOH or EtOH): mp 107–108°; ir 2.99, 5.79, and 6.08–6.15 μ (doublet); uv 230 nm (ε 31,860), 262 (8700), and 403 (7340); nmr ($CDCl_3$) δ 8.7 (t, 1, $J$ = 4.5 Hz, $D_2O$ exchange, NH), 8.2–6.6 (m, 7, ArH), 3.7 (s, 3, ester $CH_3$), and 2.93 (d, 3, $J$ = 4.5 Hz, collapses to s on $D_2O$ exchange of NH, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{14}ClNO_3$: C, 63.26; H, 4.65; N, 4.61. Found: C, 63.40; H, 4.77; N, 4.53.

**Phthalimidinospiro[3,4′]-1-methyl-2-oxo-6-chloro-1,2,3,4-tetrahydroquinazoline (30c).**—Fusion of 5 g of **29c** and 6 g of urea at 210° for 1.2 hr gave, on trituration of the cooled melt with ether or ethanol, 3.1 g of crystals, mp *ca.* 330° dec. A sample recrystallized from aqueous DMF had mp 338–340° dec; ir bonded NH (3.18, 3.27), 5.83, and 5.97 μ; uv 250 nm (ε 17,400) and 296 (2130) with inflection at 211 (41,920).

*Anal.* Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.13; H, 3.95; N, 13.40.

**Compound 30a**, similarly prepared from **29a** (R′ = $CH_3$) and recrystallized from ethanol, had mp 304–305° (lit.[42] mp 305°); ir bonded NH (3.14), 3.28, and 5.90–5.98 μ (doublet); uv 241 nm (ε 14450) and 284 (2250) with inflection at 289 (1990).

**Phthalido-3-spiro[3,4′]-1-methyl-1,2-dihydro-3,1-benzoxazine (31).**—A suspension of acid **29b** (R′ = H) (2.7 g) and paraformaldehyde (1.2 g) in 20 ml of glacial HOAc was warmed on a steam cone for 10 min. The resulting solution was allowed to stand for 3 hr and cool. Addition of 100 ml of water gave a nearly colorless oil which solidified and was collected, washed with water, and dried: 3.1 g of crystals; mp 150–152.5°, raised on recrystallization from ether or ethanol to 152–154°; ir 5.66 μ; uv 283 nm (ε 2290) and 301 (2510) with a series of inflections at 212, 230, and 244; nmr ($CDCl_3$) δ 8.1–6.6 (m, 8, ArH), 4.93 (q, 2, $J_{AB}$ = 9 Hz, methylene), and 3.1 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24 Found: C, 71.99; H, 5.14; N, 5.01.

The same compound was obtained when KCN was also added to the reaction.

***N*-Bromoacetylamino(keto ester) 32a (R′ = $CH_3$).**—Compound **29a** (R′ = $CH_3$) (2 g) in 300 ml of dry ether and 1 ml of $Et_3N$ was treated with 2 ml of $BrCH_2COBr$ with swirling, and the suspension was allowed to stand for 1 hr. After washing with water, drying ($MgSO_4$), and evaporating the ether, there was obtained 2.1 g of crystals: mp 144–146°; ir 3.20 (weak), 5.83, 5.97, and 6.04 μ; uv 233 nm (ε 27,450), 264 (12,360), and 325 (5420); nmr ($CDCl_3$) δ 11.5 (s, 1, $D_2O$ exchange, NH), 8.6–7.0 (m, 8, ArH), 4.31 (s, 2, methylene), and 3.60 (s, 3, ester $CH_3$).

*Anal.* Calcd for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.29; H, 3.79; N, 3.74.

***N*-Bromoacetylamino(keto acid) 32b (R′ = H).**—A solution of 4.8 g of **29b** (R′ = H) in 30 ml of THF was treated with 2 ml of $BrCH_2COBr$ and the suspension was let stand for 1 hr. Filtration gave **29b** (R′ = H) hydrobromide as colorless crystals from ethanol: mp 212–214° dec; ir 3.70, 4.19, 5.91 and 6.02–6.07 μ (doublet); uv 226 nm (ε 26,430), 261 (7950), and 390 (7250).

*Anal.* Calcd for $C_{15}H_{14}BrNO_3$: C, 53.59; H, 4.20; N, 4.17. Found: C, 53.83; H, 4.06; N, 3.90.

The filtrate was diluted with ether, filtered clear, and evaporated and the residue was recrystallized from ethyl acetate–ether as rather unstable, pale yellow crystals of **32b** (R′ = H), mp 143–145°, ir 5.85, 6.01, 6.16, and 6.28 μ.

*Anal.* Calcd for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.26; H, 4.07; N, 3.67.

***N*-Bromoacetylamino-*N*-methyl(keto ester) 32b (R′ = $CH_3$).**—Similar acylation of 10.7 g of **29b** (R′ = $CH_3$) in 300 ml of dry ether and 5 ml of $Et_3N$ with 9.8 ml of $BrCH_2COBr$ gave 12.7 g of crude, pale yellow, glassy material after evaporation of the water-washed and dried ether solution, crystallizing in the presence of ether to give colorless crystals: mp 96–97.5°; ir 5.83 and 5.97–6.01 μ (doublet); uv inflections at 230 nm (ε 16,360), 274 (2950), and 284 (2780); nmr ($CDCl_3$) δ 8.1–7.2 (m, 8, ArH), 3.72 (s, 5, methylene and ester $CH_3$), and 3.2 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{16}BrNO_4$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.21; H, 4.30; N, 3.68.

Bromoacetylation of **29c** (R′ = H and $CH_3$) was conducted similarly; the crude *N*-bromoacetyl derivatives **32c** were usually not purified but converted directly to **34b** and **35b**, respectively.

Crude **32c** (R′ = $CH_3$) had ir 5.79 and 5.96–5.99 μ; uv 211 nm (ε 32,800), 397 (870), and inflections at 233 (21,810) and 284 (3350).

**Methyl *o*-(2-*N*-Cyanomethyl-*N*-methylamino)benzoylbenzoate (33b).**—To 30.4 g of ester **29c**, 9 g of paraformaldehyde, and 19.5 g of KCN was added 250 ml of glacial HOAc. The mixture was stirred for 5 hr and warmed gently to an average temperature of *ca.* 45–50° during this period. After addition of water to the cooled solution, the oil was extracted with ether, washed thrice with water, and dried ($Na_2SO_4$). Evaporation gave 38 g of turbid, pale yellow oil which crystallized slowly on standing. Trituration with methanol and recrystallization from ethanol gave pale yellow crystals: mp 75.5–78°; ir 5.87 and 6.04 μ; uv 238 nm (ε 19,950) and 368 (1680); nmr ($CDCl_3$) δ 8.0–7.0 (m, 7, ArH), 4.01 (s, 2, methylene), 3.73 (s, 3, ester $CH_3$), and 2.82 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.26; H, 4.46; N, 8.08.

**Compound 33a.**—Similarly conducted Strecker reaction of **29b** (30 g) with intermittent warming on a steam cone for 5 hr gave 35.5 g of viscous, yellow oil which did not crystallize: ir 5.79 and 6.00 μ (no NH band); uv 235 nm (ε 18,220) and 362 (1770).

**Phthalido-3-spiro[3,5′]-1-methyl-2-oxo-2,3-dihydro-4,1-benzoxazepine (34a).**—Crude **32b** (R′ = H), from bromoacetylation of 2 g of **29b** (R′ = H), was treated with 125 ml of saturated ethanolic $NH_3$. The deep red solution was allowed to stand for 1 hr, then evaporated on a steam cone, and the residue was treated with dilute $NH_4OH$. An ether extract of the resulting oil was washed with water, dried ($MgSO_4$), and evaporated, giving 0.9 g of crystals, from ether: mp 176–178°; ir 5.73 and 5.98 μ; uv inflection at 276 nm (ε 3160); nmr ($CDCl_3$) δ 7.9–6.8 (m, 8, ArH), 4.45 (q, 2, $J_{AB}$ = 12 Hz, methylene), and 3.46 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 69.13; H, 4.47; N, 4.54.

**Compound 34b** was prepared similarly. Bromoacetylation of 5.8 g of **29c** (R′ = H) in 50 ml of THF and 3 ml of $Et_3N$ with 2.5 ml of $BrCH_2COBr$, filtration, and evaporation of the solution gave crude **32c** (R′ = H). Crude **32c** was treated with a solution of 5 ml of $Et_3N$ in 100 ml of ethanol. The solution, after standing overnight, was evaporated, the residue was triturated with dilute $NH_4OH$, and the product was collected, washed with water, and recrystallized from ethanol to give 4.4 g of colorless crystals: mp 183–185°; ir 5.76 and 5.96 μ; uv 282 nm (ε 2510) with inflection at 212 (40,650); nmr ($CDCl_3$) δ 8.0–6.8 (m, 7, ArH), 4.46 (q, 2, $J_{AB}$ = 12 Hz, methylene), and 3.43 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; N, 4.25. Found: C, 62.08; H, 3.75; N, 4.22.

**5-Methyl-6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione (35a).**—Crude **32b** (R′ = $CH_3$) from bromoacetylation of 10 g of **29b** (R′ = $CH_3$) was treated with 300 ml of saturated methanolic $NH_3$. The solution was allowed to stand overnight at room temperature and evaporated on a steam cone to a volume of *ca.* 80 ml, and the crystals which separated from the concentrated red solution were collected, washed with methanol and water, and air dried, giving 4.4 g (40%) of colorless crystals: mp 234–236° dec (with vigorous gas evolution, deep purple melt), raised to 237–239° dec on careful recrystallization from methanol; ir 2.97 (moderate), 5.85, and 6.08 μ; uv 230 nm (ε 17,130) and 246 (14,290), with inflection at 214 (31,410); nmr (DMSO) δ 7.9–6.8 (m, 9, 1 $D_2O$ exchange, ArH and OH), 3.88 (q, 2, $J_{AB}$ = 13 Hz, methylene), and 3.32 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.35; H, 4.85; N, 9.63.

**Compound 35b.**—Crude bromoacetyl product **32c** (R′ = $CH_3$), from 11.0 g of **29c** (R′ = $CH_3$) with 7 ml of $BrCH_2COBr$ in 500 ml of ether and 11 ml of $Et_3N$, was treated similarly with 350 ml of methanolic $NH_3$ to give 5.9 g (50%) of colorless crystals (from methanol): mp 239–241° dec; ir 3.07 (moderate), 5.87, and 5.96 μ; uv 250 nm (ε 17,540) with inflection at 230 (15,920); nmr (DMSO) δ 7.9–6.8 (m, 8, 1 $D_2O$ exchange, ArH and OH), 3.96 (q, 2, $J_{AB}$ = 13 Hz, methylene), and 3.36 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.30; H, 4.09; N, 8.51.

**6,7-Dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione.**—Compound **32a** (R′ = H) (15.9 g) was treated with

1.3 l. of saturated, methanolic $NH_3$. The suspension was stirred for 20 hr, and the resulting solution was evaporated to a volume of *ca.* 50 ml. The crystals which separated were collected, washed with ethanol and several portions of water, and dried, yield 1.2 g of colorless crystals, mp 227–229° dec. The compound was recrystallized with difficulty from methanol: mp 253–255° dec; ir 3.04, 3.10, 3.20, and 5.87–5.90 $\mu$ with shoulders at 5.83 and 5.99 $\mu$; uv inflections at 216 nm ($\epsilon$ 33,610) and 282 (2890).

*Anal.* Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.58; H, 4.62; N, 9.84.

Hydrogenolysis of this compound in glacial HOAc in the presence of 10% Pd/C at 60° gave **6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione** as colorless crystals from ethanol: mp 269–273° dec; ir 3.12–3.20, 5.83, and 5.96 $\mu$; uv 222 nm ($\epsilon$ 20,500) and 230 (20,980) with inflections at 236 (18,390) and 278 (2720); nmr (DMSO) $\delta$ 10.3 (s, 1, $D_2O$ exchange, NH), 7,9–7.0 (m, 8, ArH), 6.04 (s, 1, methine), and 4.17 (q, 2, $J_{AB}$ = 15 Hz, methylene).

*Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.87; H, 4.96; N, 10.50.

**5-Methyl-6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]-benzodiazepin-9(13b*H*)-one (35c).**—A solution of 8.3 g of **33a** in 200 ml of $NH_3$-saturated ethanol was hydrogenated (45 lb) at room temperature in the presence of washed Ni catalyst for 8 hr, uptake of *ca.* 1.5 molar equiv of $H_2$ being observed. After evaporation of the filtered solution, trituration of the residue with ether gave 6.5 g of impure solid which crystallized in the presence of methanol or ethanol and afforded 1.3 g (17%) of pale yellow crystals, mp 175–177°. Alternatively, the crude residue from evaporation was treated with water and the product was extracted with ether. A pure sample (from ethanol) had mp 179–180°; ir 3.00 and 5.94 $\mu$; uv 215 nm ($\epsilon$ 24,780) and 250 (8710); nmr ($CDCl_3$) $\delta$ 7.9–6.8 (m, 9, 1 $D_2O$ exchange, ArH and OH), 4.2–3.1 (m, 4, $CH_2CH_2$), and 2.91 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.47; H, 5.92; N, 9.68. Found: C, 72.84; H, 5.75; N, 9.99.

The compound dissolved in 15% HCl giving a deep blue solution ($\lambda_{max}$ 580, and 752 nm) which on standing for several hours became greenish yellow ($\lambda_{max}$ 435, 590, and 775 nm).

**Compound 35d.**—Similar Ni-catalyzed hydrogenation of 11.3 g of **33b** in ethanolic $NH_3$ (7 hr) gave *ca.* 1 g (10%) of colorless crystals (from ethanol): mp 187–189° dec; ir 3.09 and 5.91 $\mu$; uv 215 nm ($\epsilon$ 32,100), 255 (6750), 259 (10,710), and inflection at 301 (2010); nmr ($CDCl_3$) $\delta$ 7.9–6.9 (m, 8, 1 $D_2O$ exchange, ArH and OH), 4.1–3.0 (m, 4, $CH_2CH_2$), and 2.85 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.47; H, 5.24; N, 8.61. Found: C, 64.86; H, 4.90; N, 8.90.

Solutions of this hydroxylactam in strong acids were deep blue, becoming green on standing.

**Hydrogenolysis of 35c.**—To the deep blue solution of 1.5 g of **35c** in 220 ml of glacial HOAc was added 0.5 g of 10% Pd/C, and the suspension was shaken under $H_2$ (45 lb) at 50–55° for 1.5 hr. The filtered, nearly colorless solution was evaporated. An ether solution of the residue was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give 0.9 g of colorless crystals, mp 141–144°; a pure sample, obtained by recrystallization from methanol, had mp 144–145.5°, undepressed on admixture with **4a** prepared from **3a**; ir, uv, and nmr spectra of the independently prepared **4a** samples were identical.

Similar hydrogenolysis of **35a** in glacial HOAc with 10% Pd/C at 65° for 2 hr gave **5-methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]-benzodiazepine-6,9(13b*H*)-dione** as colorless crystals from methanol: mp 228–230°; ir 5.90 and 6.00 $\mu$; uv 230 nm ($\epsilon$ 18,900) with inflections at 222 (18,470), 237 (17,070) and 278 (2270); nmr (DMSO) $\delta$ 7.9–6.8 (m, 8, ArH), 5.99 (s, 1, methine), 3.96 (q, 2, $J_{AB}$ = 14 Hz, methylene), and 3.43 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.54; H, 5.25; N, 9.87.

**1-Methyl-2,3-dihydro-5-(2′-carbomethoxyphenyl)-1,4-benzodiazepin-2-one Hydrochloride (38a).**—Dry HCl was passed into a suspension of 3 g of **35a** in 250 ml of methanol, the saturated solution was refluxed for 0.5 hr, and most of the excess reagent was removed *in vacuo*. The residue crystallized with the aid of ether and methanol, affording 2.9 g of colorless crystals: mp 195–197° dec, not raised on further recrystallization; ir 4.44 (moderate, broad), 5.21 (moderate to weak, broad) (immonium bands), 5.81, and 5.93 $\mu$ (shoulder 5.99 $\mu$); uv 226 nm ($\epsilon$ 35,280), 285 (4930), and 350 (1230); nmr ($D_2O$) $\delta$ 8.6–7.5 (m, 8, ArH), 4.96 (m, 2, $J_{AB}$ = *ca.* 12 Hz, methylene), 4.0 (s, 3, ester $CH_3$), and 3.93 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{16}N_2O_3 \cdot HCl$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.37; H, 5.02; N, 8.00.

The corresponding **38a** base (imine), liberated from the salt with aqueous $NaHCO_3$, extracted with ether, and isolated by evaporation of the washed (water) and dried ($K_2CO_3$) solution, was a viscous, pale yellow glass: ir 5.78 and 5.96 $\mu$ (shoulders at 5.92 and 6.04 $\mu$); uv 225 nm ($\epsilon$ 35,150) and inflections at 282 (2530) and 302 (1610); nmr ($CDCl_3$) $\delta$ 8.0–6.9 (m, 8, ArH), 4.34 (q, 2, $J_{AB}$ = 12 Hz, methylene), 3.56 (s, 3, ester $CH_3$), and 3.51 (s, 3, $NCH_3$).

The imino acid corresponding to **38a** was obtained as the hydrochloride ethanolate as follows. A suspension of **35a** in *ca.* 50 parts of dry ether was saturated with dry HCl and let stand for 3 days. The crystals were collected and triturated, then recrystallized, with ethanol–ether as colorless crystals: mp 225–227.5° dec; readily soluble in water and dilute NaOH; ir broad, bonded OH band, 5.82–5.89 (broad ionic bands), and 6.06 $\mu$; uv 225 nm ($\epsilon$ 39,120), 283 (5430), and 346 (1580); nmr (DMSO) had EtOH fingerprint.

*Anal.* Calcd for $C_{17}H_{14}N_2O_3 \cdot HCl \cdot C_2H_5OH$: C, 60.55; H, 5.62; N, 7.44. Found: C, 60.67; H, 5.63; N, 7.50.

**Compound 38b Hydrochloride.**—A sample (1.2 g) of **35b** in 200 ml of methanol was treated similarly with dry HCl. The yellow solution was either refluxed for 0.7 hr or let stand for 3 days. The residue, after evaporation and trituration with several portions of ether, crystallized in the presence of ether–methanol as 0.7 g of pale yellow crystals: mp 176–184° dec, raised to 191–193° dec on recrystallization from the same solvents; ir 4.50–5.18 (immonium), 5.82, and 5.95–6.08 $\mu$; uv 227 nm ($\epsilon$ 41,250) and 312 (1980) with inflection at 284 (3180); nmr (DMSO) $\delta$ 8.5 (s, 1, $D_2O$ exchange, HCl), 8.0–7.7 (m, 6, ArH), 6.88 (d, 1, proton 6), 4.3 (m, 2, methylene), 3.53 (s, 3, ester $CH_3$), and 3.43 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{15}ClN_2O_3 \cdot HCl$: C, 57.00; H, 4.25; N, 7.39. Found: C, 56.67; H, 4.40; N, 7.32.

The base **38b**, like **38a**, was not crystalline, ir 5.83 and 5.94 $\mu$.

**2-Chloro-5-methyl-6,7-dihydro-13b-methoxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione (37b).**—Into a suspension of 1 g of **35b** in 40 ml of methanol was passed dry HCl just long enough to dissolve the crystals. On evaporation of the solution to smaller volume crystals of product separated, and were collected, washed with methanol, and dried, 0.75 g of colorless crystals, mp 211–214° dec. A sample, recrystallized from methanol, had mp 216–218.5° dec; ir 5.84 and 5.96 $\mu$; uv 231 nm ($\epsilon$ 14,460) and 251 (15,340); nmr (DMSO) $\delta$ 8.0–7.6 (m, 6, ArH), 6.96 (s, 1, proton 1), 4.0 (q, 2, $J_{AB}$ = 13 Hz, methylene), 3.33 (s, 3, $OCH_3$), and 2.86 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.16; H, 4.36; N, 8.19.

Alternatively, **37b** was prepared from **35b** using $SOCl_2$ followed by MeOH, as described in the next experiment.

**Compound 37a.**—A suspension of 2 g of **35a** in *ca.* 20 ml of $SOCl_2$ was warmed to reflux on a stream cone for *ca.* 5 min, or long enough to convert the reddish mixture to a light pink solution. The excess reagent was removed *in vacuo*, and the residue was treated immediately with methanol (*ca.* 40 ml). After the solution was warmed gently for a few minutes, the product crystallized directly from the warm solution, and was collected, washed with methanol and dried: yield 1.5 g of colorless crystals, mp 213–215° dec, raised on recrystallization from methanol to 236–237.5° dec; ir 5.84 and 5.97 $\mu$; uv 231 nm ($\epsilon$ 15,340) and 246 (12,400); nmr ($CDCl_3$) $\delta$ 8.1–6.9 (m, 8, ArH), 4.12 (q, 2, $J_{AB}$ = 12.5 Hz, methylene), 3.46 (s, 3, $OCH_3$), and 2.97 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.35; N, 9.09. Found: C, 70.16; H, 5.18; N, 8.98.

Attempts to isolate the intermediate 13b-chloro compound in crystalline form were not successful.

**1-Methyl-3-phenylindole-2-carbonitrile-2′-carboxylic Acid (36a) (R = H).**—Crude **33a** (21 g) was treated with a solution of 4.3 g of Na in 300 ml of methanol, and the solution was refluxed for 1.6 hr. Most of the methanol was removed by distillation *in vacuo*, the residue was dissolved in water and the filtered solution was acidified with dilute HCl, and the product was collected, washed with water, and air dried, 17.5 g (93%), mp 200–202°. Recrystallization from aqueous ethanol and benzene gave pale yellow crystals: mp 198–200°; ir 4.48 (moderate to

intense) and 5.88 μ; uv 224 nm (ε 36,400) and 290 (14,450), inflection at 310 (4710).

*Anal.* Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.03; H, 4.57; N, 9.83.

**Acid 36b (R = H)** was prepared similarly from **33b** with methanolic $NaOCH_3$ (refluxed 3 hr) in a yield of 84%, mp 235–240°. Recrystallization from aqueous ethanol gave bright yellow crystals: mp 241–243°; ir 4.48 (moderate to intense) and 5.91 μ; uv 233 nm (ε 41,910), 296 (13680), and 321 (8610).

*Anal.* Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.70; H, 3.57; N, 9.02. Found: C, 65.51; H, 3.60; N, 9.13.

**3-(2′-Carbomethoxyphenyl)-1-methylindole-2-carbonitrile (36a) (R = $CH_3$).**—Solution of 17.5 g of **36a** (R = H) in 1 l. of saturated methanolic HCl was let stand for 2 days, the excess reagent was distilled *in vacuo*, and the crystals were collected, 17.8 g (96%) of pale yellow needles, mp, 162–165°, giving colorless needles, mp 165–166° on recrystallization from methanol: ir 4.46 (strong) and 5.82 μ; uv 222 nm (ε 37,190) and 290 (13,990); nmr ($CDCl_3$) δ 8.2–7.0 (m, 8, ArH), 3.86 (s, 3, ester $CH_3$), and 3.62 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.72; H, 5.00; N, 9.52.

**Ester 36b (R = $CH_3$)**, prepared similarly from **36b** (R = H) in 94% yield, had mp 178.5–180° after recrystallization from ethanol; ir 4.47 (strong) and 5.77 μ; uv 233 (ε 43,250), 293 (13,490), and 322 (8720); nmr ($CDCl_3$) δ 8.1–7.4 (m, 7, ArH), 3.98 (s, 3, ester $CH_3$), and 3.63 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.64; H, 4.20; N, 8.62.

Dicarboxylic acid corresponding to **36a** was obtained *via* a diester corresponding to **33a**, as follows.

**A. Esterification.**—A solution of 1.9 g of **33a** in 50 ml of saturated, methanolic HCl was let stand for 5 days; after distillation of the methanol and addition of water, the neutral product was isolated as usual as an oil, ir 5.79 (intense) and 6.03 μ, uv 238 nm (ε 19,420) and 382 (3050).

**B. Closure to Indole.**—Crude A (0.9 g) with a solution of 0.2 g of Na in 30 ml of methanol was refluxed for 1.5 hr and the acidic product (**36a**, R = H; COOH and COOMe in place of CN) was isolated as described for **36a** (R = H) as 0.7 g of pale yellow solid, mp 212–215° dec, consisting of a mixture of diacid and acid ester. The latter could be separated by means of ether and recrystallized from the same solvent as crystals: mp 172–175°; ir 3.04, 5.81, and 5.96 μ; uv 223 nm (ε 30,910) and 296 (14,600), inflection at 316 (8960).

**C. Hydrolysis** of crude B by 3-hr reflux with 20 ml of 20% NaOH and acidification of the diluted, filtered solution gave the diacid as crystals from aqueous ethanol: mp 249–251° dec; ir 5.90 and 5.97–6.00 μ; uv 220 nm (ε 37,220) and 294 (14,120); nmr (DMSO) δ 12.5 (broad, 2, $D_2O$ exchange, both COOH), 8.0–7.0 (m, 8, ArH), and 4.02 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.89; H, 4.54; N, 5.06.

**2-Chloro-5-methylindolo[2,3-*d*][2]benzazepin-8(6*H*)-one (39b).**—Owing to low solubilities of respective materials in alcohols, poor results were obtained in nickel reduction of ester nitriles **36** in amounts greater than a few grams in ethanolic ammonia and similar media. For larger scale work, therefore, the following procedure was used. A solution of 11.2 g of **36b** in 400 ml of $NH_3$-saturated glycol monoethyl ether (Cellosolve) and 50 ml of DMF, together with *ca.* 10 g of water- and alcohol-washed Grace 28 nickel catalyst, was shaken under $H_2$ (45 lb) at 50° for 8 hr, or until absorption ceased. The filtered solution on evaporation gave a crude residue from which 4.6 g of lactam **39b**, mp 301–303°, was isolated directly by trituration with ether. The oily residue remaining after evaporation of the filtrate was heated to 170° (oil bath) for *ca.* 15 min and cooled, and the solid was triturated with ether to give 4.1 g of additional lactam, bringing the yield of **39b** to 8.7 g (85%). Recrystallization from ethanol gave colorless needles: mp 310–312°; ir 3.03–3.10 (bonded), 6.09, and 6.21–6.26 μ; uv 234 nm (ε 38,380) and 275 (13,250) with inflections at 216 (30,060), 291 (10,830), and 304 nm (10,180).

*Anal.* Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.41; N, 9.44. Found: C, 68.77; H, 4.42; N, 9.49.

In a similar reduction of **36b** (2 g) in ammoniacal DMF–ethanol (200 ml) at 30° there was isolated a fairly pure sample of the intermediate amino ester, **2-aminomethyl-3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindole**, as colorless crystals (from ether): mp 98–100°; ir NH highly bonded, visible only in solution (chloroform) spectra, and 5.79 μ; uv 231 nm (ε 80,710) and 286 (17,700) with inflection at 304 (15,710); nmr ($CDCl_3$) δ 8.0–7.0 (m, 7, ArH), 3.81 (s, 2, methylene), 3.72 (s 3, ester $CH_3$), 3.52 (s, 3, $NCH_3$), and 1.24 (s, 2, $D_2O$ exchange, $NH_2$).

*Anal.* Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 66.18; H, 5.51; N, 8.52.

When the $NH_3$ was omitted in a similar hydrogenation of 8.9 g of ester nitrile **36b**, there were obtained 2.3 g of lactam **39b** and from the ether filtrate 4.5 g of secondary amine, **bis[3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindolyl-2-methyl]amine**, as colorless crystals from ethanol: mp 166–168°; ir 5.78 μ; uv 230 nm (ε 58,410) and 314 (27,670).

*Anal.* Calcd for $C_{36}H_{31}Cl_2N_3O_4$: C, 67.50; H, 4.88; N, 6.56. Found: C, 67.53; H, 4.56; N, 6.48.

**Lactam 39a** was obtained by similar nickel-catalyzed hydrogenation of **36a** in the presence of ammonia in alcohol, DMF, or cellosolve, and thermal closure of crude, intermediate amino ester. Recrystallization from ethanol afforded colorless crystals: mp 309–311°; ir 3.12 (broad, weak), 6.07, and 6.21 μ; uv 227 nm (ε 36,660), 274 (11,130), and 284 (10,920) with inflection at 215 (30,740); nmr (DMSO) δ 8.5–7.0 (m, 9, 1 $D_2O$ exchange, ArH and NH), 4.22 (d, 2, $J \cong 6$ Hz, collapse to s on $D_2O$ exchange of NH, methylene), and 3.8 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.20; H, 5.62; N, 10.33.

When nickel-catalyzed hydrogenation of **36a** (21 g) was carried out in DMF, omitting the $NH_3$, the crude product contained *ca.* 3 g of lactam **39a** and the remainder of the material was a mixture of basic esters and partly reduced substance (imine), ir 5.80–5.83 and 6.14 μ. Treatment of the crude solid with 30% aqueous HCl and recrystallization of the resulting, water-washed, crude crystals from ether and ethanol gave **3-(2′-carbomethoxyphenyl)-1-methylindole-2-carboxaldehyde**: mp 117–119°; ir 5.80 and 6.00 μ; uv 227 nm (ε 21,490) and 314 (18,420) with inflection at 350 (7110); nmr ($CDCl_3$) δ 9.7 (s, 1, CHO), 8.2–7.0 (m, 8, ArH), 4.16 (s, 3, ester $CH_3$), and 3.54 (s, 3, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 74.01; H, 5.28; N, 5.10.

***N*-Methyl Lactam 39c (X = H).**—Lactam **39a** (3 g) was added to 0.85 g of 56% NaH in 10 ml of DMF, and the red, effervescent mixture was treated with 2 ml of iodomethane. When the exothermic reaction subsided, 2 ml of additional $CH_3I$ was added and the suspension was stirred for 3 hr. Water was added, and the crude product (3 g) was collected, washed with water, air dried, and triturated with ether to give 2.0 g of crystals: mp 251–253°, raised to 253–255° on recrystallization from ethanol; ir 6.19 μ; uv 215 nm (ε 30,020), 228 (36,950), 271 (11,460), 282 (10,730) and 291 (10,630); nmr (DMSO) δ 7.9–7.0 (m, 8, ArH), 4.46 (s, 2, methylene), 3.88 (s, 3, indole $NCH_3$), and 3.13 (s, 3, lactam $NCH_3$).

*Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.55; H, 5.71; N, 10.23.

***N*-Methyl Lactam 39c (X = Cl).**—Similar methylation of **39b** in the presence of NaH afforded colorless crystals (from DMF–ethanol): mp 315–316°; ir 6.21 μ; uv 234 nm (ε 38,600), 274 (13,490), 290 (10,460), and 303 (10,440).

*Anal.* Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; N, 9.02. Found: C, 69.48; H, 4.85; N, 8.96.

**Lactam 39d (X = Cl, *n* = 2).**—To 3.0 g of **39b** in 30 ml of DMSO was added 1.5 g of potassium *tert*-butoxide, then 20 ml of 1.8 *M* solution of β-dimethylaminoethyl chloride in toluene. The mixture was stirred for 6 hr at *ca.* 75°; 5 ml additional chlorodimethylaminoethane reagent was added; and the mixture was let stand for 1–2 days. After addition of water, a benzene extract of crude material was washed (three portions of water), dried ($K_2CO_3$), and evaporated. Trituration of the crude residue with ether gave 1.5 g of crystals: mp 224–225° before and after recrystallization (EtOH); ir 6.18 μ; uv 235 nm (ε 38,720), 275 (13,680), 290 (10,500), and 301 (10,310); nmr ($CDCl_3$) δ 8.1–7.1 (m, 7, ArH), 4.4 (s, 2, lactam methylene), 3.78 (s, 3, indole $NCH_3$), 3.70 (t, 2, $J$ = 7 Hz, chain $CH_2$ attached to lactam N), 2.48 (t, 2, $J$ = 7 Hz, methylene adjacent to $NMe_2$), and 2.2 (s, 6, $NMe_2$).

*Anal.* Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42. Found: C, 68.58; H, 5.97; N, 11.62.

**Lactam 39d (X = Cl, *n* = 3).**—Similar potassium *tert*-butoxide mediated alkylation of **39b** with 1-chloro-3-dimethylaminopropane gave, after recrystallization from benzene, crystals, mp 180–181°, ir 6.18–6.25 μ, uv and nmr like those of the preceding compound.

*Anal.* Calcd for $C_{22}H_{24}ClN_3O$: C, 69.19; H, 6.33; N, 11.00. Found: C, 69.30; H, 6.40; N, 10.77.

Alkylation of **39a** and b with basic halides in the presence of NaH was less satisfactory.

**Registry No.**—**1b** amidoxime 2HCl, 36271-17-7; **1c**, 36271-18-8; **1d**, 36271-19-9; **1e**, 36208-00-1; **1e** amidoxime, 36271-20-2; **2a** HCl, 36271-21-3; **2b** HCl, 36271-22-4; **2c** 2HCl, 36271-23-5; **2e** 2HCl, 36271-24-6; **4a**, 36271-25-7; **4b**, 36271-26-8; **4c**, 36271-27-9; **4d**, 36271-28-0; **4e**, 36271-29-1; **5a**, 36271-30-4; **5a** HCl, 36271-31-5; **5b**, 36271-32-6; **5b** HCl, 36271-33-7; **5c** HCl, 36271-34-8; **5e** HCl, 36271-35-9; **6**, 36271-36-0; **6** HCl, 36271-37-1; **8b**, 36258-91-0; **9b**, 36258-92-1; **11**, 36207-97-3; **12a**, 36270-92-5; **12b**, 36270-93-6; **13**, 36270-94-7; **14**, 36270-95-8; **16**, 4015-28-5; **16** dihydro formic acid salt, 36270-97-0; **17**, 36270-98-1; **18a**, 36270-99-2; **18b**, 36271-00-8; **18c**, 10456-63-0; **18d**, 36271-02-0; **19**, 36207-98-4; **21b**, 36271-03-1; **22**, 36271-04-2; **23**, 1022-13-5; **24**, 36271-06-4; **24** amide, 36271-07-5; **25**, 2898-12-6; **25** HCl, 2898-11-5; **26a**, 24139-18-2; **26b** HCl, 36271-11-1; **26c** HCl, 21139-23-1; **26d**, 21139-24-2; **28b**, 3311-40-8; **28c**, 16219-18-4; **28d**, 36271-15-5; **28e**, 36271-16-6; **29a** (R′ = $CH_3$), 36259-21-9; **29b** (R′ = H), 36259-22-0; **29b** (R′ = H) *N*-chloroacetyl derivative, 36259-23-1; **29b** (R′ = H) HBr, 36259-24-2; **29b** (R′ = $CH_3$), 36259-25-3; **29c** (R′ = H), 16175-35-2; **29c** (R′ = $CH_3$), 36259-27-5; **29d** (R′ = H), 36259-28-6; **29e** (R′ = H), 36259-29-7; **29e** (R′ = $CH_3$), 36259-30-0; **30c**, 36208-04-5; **31**, 36259-31-1; **32a** (R′ = $CH_3$), 36259-32-2; **32b** (R′ = H), 36259-33-3; **32b** (R′ = $CH_3$), 36259-34-4; **33b**, 36259-35-5; **34a**, 36259-36-6; **34b**, 36258-42-1; **35a**, 36258-43-2; **35b**, 36258-44-3; **35c**, 36258-45-4; **35d**, 36258-46-5; **36a** (R = H), 36258-47-6; **36a** (R = $CH_3$), 36258-48-7; **36a** dicarboxylic acid, 36258-49-8; **36b** (R = H), 36258-50-1; **36b** (R = $CH_3$), 36258-51-2; **37a**, 36258-52-3; **37b**, 36258-53-4; **38a**, 36208-05-6; **38a** HCl, 36258-54-5; **38a** imino acid HCl, 36258-55-6; **38b** HCl, 36258-56-7; **39a**, 36258-57-8; **39b**, 36258-58-9; **39c** (X = H), 36258-59-0; **39c** (X = Cl), 36258-60-3; **39d** (X = Cl, $n$ = 2), 36258-61-4; **39d** (X = Cl, $n$ = 3), 36258-62-5; i, 36258-63-6; *p*-chloroanilinoacetonitrile, 24889-92-7; *p*-chloroanilinoacetamide, 21979-12-4; *N*-acetyl-*p*-chloroanilinoacetonitrile, 36258-66-9; *p*-chloro-*N*-acetylanilinoacetonitrile amidoxime, 36258-67-0; 4-*N*-benzylideneaminoveratrale, 13548-24-8; 2,3-dimethoxy-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine HCl, 36258-69-2; 2-(α-hydroxybenzyl)-4-chloroanilinoacetonitrile, 36258-70-5; 6-chloro-1,2-dihydro-2,2-dimethylquinazoline 3-oxide, 4844-66-0; *N*-(2-aminoethyl)-*N*-methyl-2-benzoyl-4-chloroaniline hydrochloride, 36258-72-7; 6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione, 36258-73-8; 6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione, 36258-74-9; 5-methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9(13b*H*)-dione, 36258-75-0; 2-aminomethyl-3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindole, 36258-76-1; bis[3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindolyl-2-methyl]-amine, 36258-77-2; 3-(2′-carbomethoxyphenyl)-1-methylindole-2-carboxaldehyde, 36258-78-3; *N*-methyl-*m*-methoxyacetanilide, 36258-79-4.

**Acknowledgment.**—We are indebted to Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Natalie Cahoon, Mr. Charles Navarro, Mr. Mike Hotolski, Mr. Anis Hamden, and Miss Barbara Biffar of the staff of Mr. Louis Dorfman for microanalytical and spectral data, to Mr. Robert Dziemian and Miss Ann Smith for large-scale preparation of certain intermediates, to Mrs. Angela Aretakis and Dr. John Marsh for some literature search work, and especially to Miss Ruth Behnke for precise nmr spectra and their interpretation. Discussion of various phases of the effort with Dr. Neville Finch is cordially acknowledged.

# Heterocyclic Studies. 37. Rearrangements of a Dihydro-1,2-diazepin-4-ol and 1,2-Diazabicyclo[3.2.0]hepten-6-ol to a Tetrahydropyridazine

SAMUEL M. ROSEN AND JAMES A. MOORE*

*Department of Chemistry, University of Delaware, Newark, Delaware 19711*

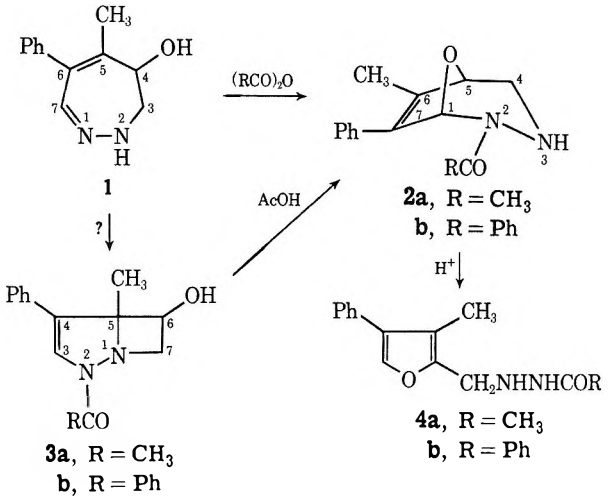
*Received June 19, 1972*

Acylation of diazepinol **1** in the presence of weak organic bases gives the oxides **2**; the bicyclo[3.2.0]alcohols **3** rearrange to **2**, but are not intermediates in the conversion **1** → **2**. With triethylamine, acylation of **1** gives the 4-formyltetrahydropyridazines **5**, which are also obtained by thermal rearrangement of **3**. The tetrahydropyridazines are converted by successive oxidation and deacylation to 4-methyl-5-phenylpyridazine (**9**). The reaction of **1** and **3** are suggested to occur *via* an acyldiazepinium cation–acylbetaine system (**10**–**12**).

The preparation and interconversion of the diazepinol **1**, bicyclo[3.2.0] alcohol **3a**, and bridged oxide **2a** were reported some time ago.[1] The bicyclic alcohol **3a**, obtained by reduction of the corresponding ketone, is converted by mild acid to the oxide **2a**; the latter is also produced by acetylation of **1**. The noncrystalline acetate ester of **3a** was obtained in impure form by acetylation of **1** in the presence of pyridine, and **3a** was suggested as an intermediate in the conversion of **1** to **2**. A terminal acid-catalyzed elimination leads from **2** or **3** to furfurylhydrazine derivatives **4**. Further work in this series has extended our understanding of these reactions and has revealed an important rearrangement process which was missed in the earlier work.

To provide more complete characterization of the [3.2.0] bicyclic alcohols, the *N*-benzoyl alcohol **3b** was prepared and converted to the crystalline acetate and benzoate esters. As in the acetyl series, a single epimeric alcohol was produced in the reduction of the benzoyl[3.2.0] ketone; the hydroxyl configuration is assumed to be endo from the expected exo attack of

(1) J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).

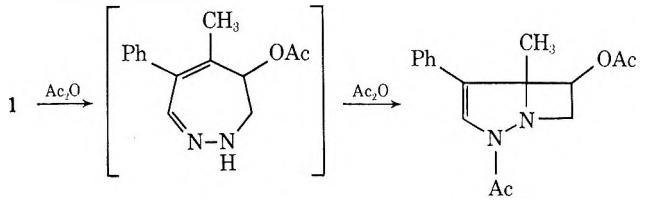



hydride. The bridged oxide **2b** and the corresponding furan **4b** were obtained under conditions similar to those used in the acetyl series.

**Acylation of Diazepinol 1.**—To clarify the formation of [3.2.0] bicyclic alcohols **3** from **1**, and possibly find a route to the exo isomers of **3**, benzoylation of the diazepinol **1** was carried out under a variety of conditions. With benzoyl or acetyl chloride and pyridine or dimethylaniline, only the bridged oxides **2** were isolated; the nmr spectrum of the total product from benzoyl chloride indicated traces of **3b** and the benzoate ester. Reinvestigation of the reaction of **1** with acetic anhydride–pyridine revealed a very complex mixture which was analyzed by nmr. The relative areas of methyl peaks showed nearly equal amounts of **3a** (as its acetate), **2a** (as such and as the N-3 acetyl derivative), and a third component (**5a**, discussed below, plus its N-2 acetyl derivative).

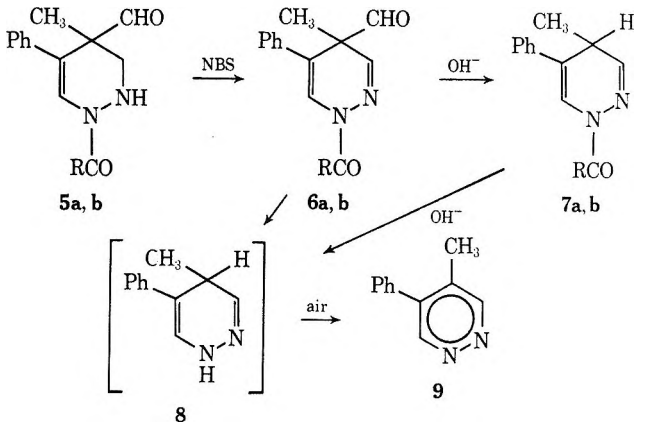
Although the [3.2.0] alcohols **3** are readily transformed to the oxides **2** with acetic acid or with the hydrochlorides of pyridine or dimethylaniline, it was found that this isomerization is *not* the major pathway to the oxides in these acylations. A reaction of **1** and benzoyl chloride which was quenched with ammonia after a few minutes gave only **2b** and unreacted **1**, and in an experiment with equimolar amounts of the diazepinol **1** and [3.2.0] alcohol **3b** with 1 equiv of benzoyl chloride **1** was completely converted to **2b** without significant isomerization of the bicyclic alcohol.

These results establish that attack of acid chlorides on the diazepinol **1**, paralleling the corresponding diazepinone,[2] occurs predominantly at N-1, with the oxides **2** arising by direct internal nucleophilic attack at C-7 by the hydroxyl group, without intermediacy of the [3.2.0] alcohol. The minor formation of **3a** acetate observed with acetic anhydride seems best accounted for by initial acetylation of the hydroxyl group of **1** followed by attack at N-1; in this case, bridging to the [3.2.0] system is the only path available.




(2) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 35 (1966).

CHART I




able. An attempt to isolate the diazepinol *O*-acetate by using insufficient acetic anhydride was unsuccessful.

When triethylamine rather than pyridine or dimethylaniline was used as the acid acceptor in the reaction of diazepinol **1** with benzoyl chloride, an entirely different reaction occurred, and the tetrahydropyridazine aldehyde **5b** (Chart I) was the only product isolated. With acetyl chloride and triethylamine, a mixture of the oxide **2a** and aldehyde **5a** was obtained. The aldehyde **5a** and its N-2 acetyl derivative were also present in the mixtures obtained with acetic anhydride. The aldehydes were found to be much more readily obtained by thermal rearrangement of the bicyclic alcohols, and this was the source of material used for characterization.

**Thermal Rearrangement of Bicyclic Alcohols.**—The *N*-benzoyl and *N*-acetyl [3.2.0] alcohols **3a** and **3b** undergo isomerization in refluxing toluene to give the respective pyridazinealdehydes **5a** and **5b** in high yields. The nmr spectra of these products contained peaks for $CH_3C<$, $-CH_2-$(AB), $-CH{=}N$, and CHO groups; the ir spectra showed $\nu_{NH}$ 3300 and $\nu_{CO}$ 1630 and 1710 $cm^{-1}$. Reduction of **5b** with $NaBH_4$ gave a carbinol with $\delta_{CH_3}$ shifted 0.4 ppm upfield, indicating the $CH_3CCHO$ grouping.

Structure **5b** was proven by stepwise degradation to the pyridazine **9**. This conversion requires two deacylations and two oxidations (Chart I).

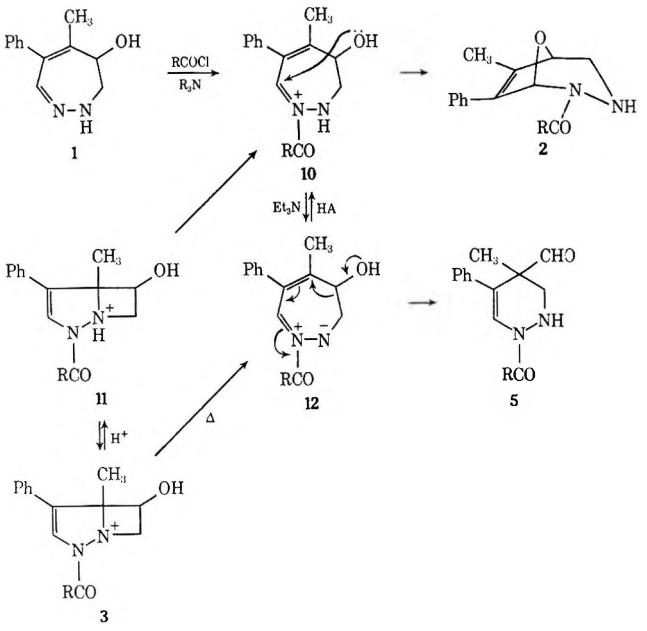
An initial oxidation with NBS proceeded very smoothly to the dihydropyridazine **6b**. Mild treatment of **6b** with base unexpectedly caused preferential loss of the *C*-formyl group with formation of **7b** [$\delta_{CH_3}$ 1.25 (d, $J$ = 7 Hz), $\delta_{H\text{-}4}$ 3.55 (q of d, $J$ = 7.0, 3.6 Hz)]. Longer treatment of **6b** or **7b** with base gave **8** admixed with the pyridazine **9**; the nmr spectrum corresponded very closely to that of a similar preparation of **8** + **9** from a different source.[3] Air oxidation of the crude dihydropyridazine led to the crystalline pyridazine **9**, identical with an authentic sample.

## Discussion

The formation of the aldehydes by these two reactions suggests a common pathway from **1** and **2**, and the betaine **12** appears to be a logical intermediate

(3) J. A. Moore, E. J. Volker, and C. M. Kopay, *ibid.*, **36**, 2676 (1971).

CHART II

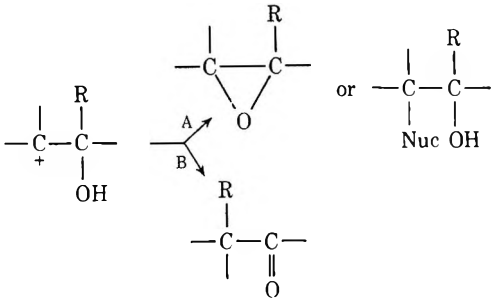



available from both starting points (Chart II). The corresponding diazabicyclo[3.2.0] ketones have been shown to give on heating analogous acyl betaines which can be trapped by dipolarophiles.[4] Similar attempts to trap **12** by heating the alcohol **3b** in dimethyl acetylenedicarboxylate resulted in a complex mixture in which only the tetramer[5] of the acetylenic ester was identified; Michael addition of the alcohol may be a complicating factor in this case.

As depicted in Chart II, the acyl betaine **12** is presumed to arise, *via* the acyl cation **10**, from diazepinol **1** when the acylation is carried out with a sufficiently strong base, *e.g.*, triethylamine. With the much weaker bases pyridine or dimethylaniline, bridging of **10** to the bicyclic oxide occurs. In this view the presence of acid in the thermal rearrangement of **3** should lead to protonation of the betaine **12** and thence to the oxide, and this was observed. Isomerization of the [3.2.0] alcohol **3b** at 110° in the presence of 1 equiv of benzoic acid produced a mixture of aldehyde and oxide (*ca.* 3:5); at 80° with 1 equiv of acid the product was almost entirely oxide.

In the isomerization of the bicyclic alcohol **3** to **2** with pyridine or dimethylaniline hydrochloride at room temperature, the diazepinium cation **10** is probably formed *via* the protonated bicyclic alcohol **11**. This process again finds a parallel in the bicyclo[3.2.0]-ketone series, in which acidic methanol brings about ring opening and coordination of alcohol at C-7.[2]

The proposed pathways to **2** and **5** from cation **10** and betaine **12**, respectively, are lacking in a number of details, but this scheme provides a rationale for the main findings. The reactions leading to **2** and **5** are formally analogous to the product-forming steps in processes such as pinacol and Tiffenau–Demjanow rearrangements, or the reactions of carbonyl compounds with diazoalkanes, *viz.*




The distribution of products between paths A and B depends upon, among several factors, the extent of electron deficiency in the system. In diazoalkane–carbonyl reactions, for example, negative substituents in the carbonyl compound increase the amount of oxide (path A), whereas alkyl substitution in the diazo compound favors path B.[6] These and related effects reflect the need for stabilization of positive charge in the transition state for migration of R (path B). This requirement should be much better met in the neutral betaine than in the acyl cation, and the product distribution in the reactions of **1** and **3** is thus consistent with the general pattern observed in this type of rearrangement.

## Experimental Section

**2-Benzoyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-ol (3b).**—To a solution of 2.00 g of 2-benzoyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one[2] in 250 ml of ethanol was added 300 mg of $NaBH_4$ dissolved in 20 ml of ethanol. After standing at 25° for 2.5 hr, the reaction mixture was neutralized with acetic acid, concentrated, diluted with water, and extracted with $CH_2Cl_2$. The organic layer was washed with water, dried, and evaporated to an oil. On addition of ether (containing a small amount of methanol) and chilling, 1.41 g (71%) of slightly yellow prisms were obtained in two crops, mp 145–147° (first crop). Recrystallization from methanol–ether gave colorless prisms of **2b**: mp 148–149°; $\nu^{KBr}$ 3300, 1620 $cm^{-1}$; $\delta^{CDCl_3}$ 1.57 (s, 3), AMX ($\delta_A$ 4.45, $\delta_M$ 4.07, $\delta_X$ 3.28, $J_{MX}$ = 9, $J_{AX}$ = $J_{AM}$ = 6.5 Hz), 3.42 (s, 1 $D_2O$ exchange), 7.2–7.9 ppm (m, 11).

*Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.63; H, 5.99; N, 9.04.

The benzoate ester of **3b** was obtained in 70% yield with benzoyl chloride–pyridine ($CH_2Cl_2$, 25°, 30 min): mp 155–156°; $\delta^{CDCl_3}$ 1.82 (s, 3), AMX ($\delta_A$ 5.44, $\delta_M$ 4.33, $\delta_X$ 3.57, $J_{MX}$ = 10, $J_{AX}$ = $J_{AM}$ = 6.5 Hz), 7.1–7.9 (m, 16).

The acetate was obtained with $Ac_2O$–pyridine, mp 152–153°, $\delta_A$ 5.27, $\delta_M$ 4.15, $\delta_X$ 3.50.

*Anal.* Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79. Found: C, 72.16; H, 5.81.

**2-Benzoyl-6-methyl-7-phenyl-8-oxa-2,3-diazabicyclo[3.2.1]-oct-6-ene (2b).**—Bicyclic alcohol **3b** (300 mg) was added to 10 ml of $CH_2Cl_2$ containing anhydrous pyridine hydrochloride prepared from 0.1 ml of pyridine. After standing for 2 hr at 25° the solution was washed with 1 *N* HCl, 5% $NaHCO_3$, and water, and was then dried and evaporated to an oil which crystallized from ether to give 208 mg (70%) of **2b** as white plates, mp 195–197°. After recrystallization from $CH_2Cl_2$–ether the melting point was 201–202°; $\nu^{KBr}$ 3300, 1630 $cm^{-1}$; $\delta^{CDCl_3}$ 2.20 (s, 3), AB pattern ($\delta_A$ 3.56, $\delta_B$ 2.65, $J_{AB}$ = 14 Hz, the A doublet was broad and flat but sharpened on addition of $D_2O$ and was split further, $J$ = 3 Hz), 4.65 (br, s, 1), 4.85 (br s, $D_2O$ exchange), 6.97 (s, 1), 7.3–7.8 ppm (m, 11).

*Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.39; H, 5.76; N, 9.27.

When *N,N*-dimethylaniline hydrochloride was used instead of pyridine hydrochloride, **2b** was obtained in 42% yield.

**1-Benzoyl-2-(3-methyl-4-phenylfurfuryl)hydrazine (4b).**—Hydrogen chloride gas was bubbled through a solution of 170 mg of

(4) O. S. Rothenberger and J. A. Moore, *J. Org. Chem.*, **37**, 2796 (1972).
(5) J. C. Kauer and H. E. Simmons, *ibid.*, **33**, 2720 (1968).
(6) C. D. Gutsche, *Org. React.*, **8**, 369 (1954).

oxide **2b** in 10 ml of $CH_2Cl_2$ for 7 min. After washing with water and $NaHCO_3$ and drying, the solution was evaporated to an oil which crystallized from ether to give 112 mg (66%) of **4b** as colorless crystals, mp 128–130°. After recrystallization from $CH_2Cl_2$–ether the melting point was 130–131°; $\nu^{KBr}$ 3250, 3300, 1650 $cm^{-1}$; $\delta^{CDCl_3}$ 2.08 (s, 3), 4.13 (s, 2), 4.65 (s, 1 $D_2O$ exchange), 7.2–7.9 (m, 11), 8.4 ppm (br s, 1 $D_2O$ exchange).

*Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.40; H, 5.81; N, 9.13.

**Reaction of 1 with Benzoyl Chloride in Triethylamine.**—Diazepinol 1 (70 mg, 0.35 mmol) was dissolved in 1 ml of $CH_2Cl_2$ containing 0.049 ml (0.35 mmol) of triethylamine, and 0.040 ml (0.35 mmol) of benzoyl chloride in 1.0 ml of $CH_2Cl_2$ was added. After standing at 0° for 30 min the reaction mixture was extracted with 1 *N* HCl, 5% sodium bicarbonate, and water. The methylene chloride layer was dried and evaporated to an oil. Addition of ether and chilling gave 26 mg (24% of off-white crystals, mp 121–125°, ir identical with that of **5b** described below.

The nmr spectrum of the crude oil obtained before the isolation of **5b** contained peaks for **5b** and also starting diazepinol 1, alcohol **3b**, oxide **2b**, and the benzoate of **3b**. A tlc of the crude oil showed zones corresponding in $R_f$ value with each of these compounds. The relative amounts were estimated from the contribution of the respective methyl peaks for each compound to the total integral of the methyl region of the nmr (Table I).

TABLE I

| Compd | $\delta^{CDCl_3}$ | Integral, mm | % of total methyl peaks |
|---|---|---|---|
| Aldehyde **5b** | 1.20 | 23 | 59 |
| Unknown | 1.28 | 2 | 5 |
| Alcohol **3b** | 1.55 | 1 | 3 |
| Diazepinol **1** + benzoate of **3b** | 1.78 | 5 | 13 |
| Unknown | 2.03 | 4 | 10 |
| Oxide **2b** | 2.13 | 4 | 10 |

In another run under similar conditions, aldehyde **3b** represented 58% of the total methyl integral. The percentages of other peaks varied by a few per cent when compared to the original experiment.

**Reaction of Diazepinol 1 with Acetic Anhydride.**—Acetylations were carried out by a standard procedure using (a) 1 equiv of $Ac_2O$ and 1 equiv of pyridine, (b) 2 equiv of $Ac_2O$ and 2 equiv of pyridine, and (c) 1 equiv of $Ac_2O$ and 1 equiv of triethylamine. Diazepinol 1, 140 mg (0.7 mmol), was treated with a solution of the $Ac_2O$ (0.066 ml in a and c, 0.13 ml in b) in 1 ml of $CH_2Cl_2$ and a solution of the appropriate amount of amine in 1 ml of $CH_2Cl_2$. After 90 min at 25° the solution was washed thoroughly with aqueous $NaHCO_3$, dilute acid, and water, dried, and evaporated to an oil. The nmr spectrum of the total product mixture was scanned (A-60) at 250 Hz and the C–Me and N– or O–COMe peaks in the products were identified by addition of compounds **2**, **3**, and **5** and their acetyl derivatives to portions of the total product mixture and noting enhancement of peaks in the spectra. The peaks corresponding to the various Me signals were then cut from copies of the spectra and weighed. The product ratios were derived by the relative weights of the sharpest Me peak (or average of two or three sharp peaks when present) for each compound. The results are summarized in Table II.

The product composition for run b (excess $Ac_2O$) was calculated as follows (Table III).

**Competition of Diazepinol 1 and Alcohol 3b for Benzoyl Chloride and Pyridine.**—To 70 ml (0.35 mmol) of diazepinol 1 and 106 ml (0.35 mmol) of bicyclic alcohol **3b** was added 1.0 ml of a $CH_2Cl_2$ solution containing 0.030 ml (0.37 mmol) of pyridine and 1.0 ml of a solution of 0.040 ml (0.35 mmol) of benzoyl chloride in $CH_2Cl_2$. After standing at 0° for 20 min the reaction mixture was extracted with water, 5% $NaNCO_3$, and water, dried, and evaporated to an oil. The nmr spectrum ($CDCl_3$) revealed a large amount of alcohol **3b** (δ 1.57 ppm, integration 50), oxide **2b** (δ 2.15 ppm, integration 34), a small amount of diazepinol 1 (δ 1.80 ppm, integration 6), and an unidentified peak at δ 1.77 (integration 3).

TABLE II

ACETYLATION OF DIAZEPINOL 1

| Compd | Peak position, Hz | Peak weights, mg — Condition: 1 $Ac_2O$–1 Pyr | 2 $Ac_2O$–2 Pyr | 1 $Ac_2O$–1 $Et_3N$ |
|---|---|---|---|---|
| *N*-2-Acetyl **5a** | 68 | 8 | 8 | |
| **5a** | 72 | 13 | 5 | 20 |
| Unknown | 75 | 9 | 10 | |
| *O*-Acetyl **3a** | 102 | 6 | 17 | 10 |
| *O*-Acetyl **3a** | 104 | 6 | 16 | 10 |
| Diazepinol **1** | 108 | 16 | | |
| *N*-3-Acetyl **2a** | 120 | | 3 | |
| *N*-3-Acetyl **2a** | 124 | | 3 | |
| *N*-2-Acetyl **5a** | 125 | 5 | 6 | |
| Mixture[a] | 129 | 26 | 31 | 11[b] |
| **2a** | 131 | 17 | 16 | |
| *N*-2-Acetyl **5a** | 132 | 9 | | |
| **5a** | 136 | 19 | 6 | 23 |
| Unknown | 142 | 18 | 16 | |

[a] Overlapping peaks from two or three compounds. [b] *N*-Acetyl of **3a** acetate.

TABLE III

| Compd | Peaks used | Av weight | Rel amount |
|---|---|---|---|
| *N*-2-Acetyl **5a** | 68, 125 | 7 | 2 |
| **5a** | 72, 136 | 6 | 2 |
| **2a** | 131 | 16 | 5 |
| *N*-3-Acetyl **2a** | 120, 124 | 3 | 1 |
| *O*-Acetyl **3a** | 102, 104 | 16 | 5 |

**1-Acetyl-4-formyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazine (5a).**—A solution of 300 mg of bicyclic alcohol **3a** in 350 ml of toluene was refluxed for 4 hr. The toluene was then removed *in vacuo* and a small amount of ether was added. Chilling gave 2.52 mg (84%) of colorless crystals of **5a**, mp 98–99°. Recrystallization from ether raised the melting point to 99–99.5°; $\nu^{KBr}$ 3300, 1710, 1630 $cm^{-1}$; $\delta^{CDCl_3}$ 1.21 (s, 3), 2.25 (s, 3), 2.7–3.6 (m, 2 $D_2O$ AB, $\delta_A$ 3.42 $\delta_B$ 2.82, $J_{AB}$ = 14 Hz), 4.63 (q, 1 $D_2O$ exchange), 7.67 (s, 1), 7.1–7.4 (m, 5), 9.90 ppm (s, 1).

*Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: 68.71; H, 6.48; N, 11.35.

The 1,2-diacetyl derivative was prepared (for authentication of nmr peaks in mixtures) with $CH_3COCl$ and dimethylaniline: mp 127–128°; $\delta^{CDCl_3}$ 1.15 (s, 3), 2.12 (s, 3), 2.25 (s, 3), 2.78 (d, 1, $J$ = 14 Hz), 4.97 (d, 1, $J$ = 14 Hz), 7.0–7.6 (m, 6), 9.58 (s, 1).

**1-Benzoyl-4-formyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazine (5b).**—A solution of 650 ml of **3b** in 250 ml of toluene was refluxed for 4 hr. Evaporation and addition of ether gave 584 mg (90%) of colorless crystals in two crops, mp (combined first and second crops) 129–130°. Recrystallization from ether–methanol gave white prisms of **5b**: mp 132–132.5°; $\nu^{KBr}$ 1630, 1710 $cm^{-1}$; $\delta^{CDCl_3}$ 1.15 (s, 3), 2.67–3.67 (m, 2, $D_2O$ AB, $\delta_A$ 3.39, $\delta_B$ 2.87, $J_{AB}$ = 13.2 Hz), 7.1–7.75 (m, 12), 9.92 ppm (s, 1).

*Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.35; H, 5.86; N, 9.09.

The 1,2-dibenzoyl derivative was prepared (65%) from 300 mg of **5b**, 0.7 ml of benzoyl chloride, and 2.7 ml of *N*,*N*-dimethylaniline in 30 ml of $CH_2Cl_2$ (30°, 6 hr): mp 173–175°; $\nu$ 1670, 1720 $cm^{-1}$; $\delta^{CDCl_3}$ 1.20 (s, 3), AB dd (calcd $\delta_A$ 3.36, $\delta_B$ 3.58, $J_{AB}$ = 6.8 Hz), 6.9–7.6 (m, 16), 9.75 (s, 1).

*Anal.* Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40. Found: C, 76.03; H, 5.39

**1-Benzoyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazine-4-methanol.**—To a solution of 368 mg (1.20 mmol) of **5b** in 60 ml of ethanol was added 56 mg of $NaBH_4$ in 20 ml of ethanol. After standing at 25° overnight, the reaction mixture was neutralized with acetic acid and evaporated. Water was then added and the mixture was extracted with ether. The ether layer was dried, concentrated, and chilled to give 272 mg (74%) of white crystals, mp 154–155°. Recrystallization from ether–acetone raised the melting point to 155.5–156°; $\nu^{KBr}$ 3200, 1610 $cm^{-1}$; $\delta^{CDCl_3}$ 0.83 (s, 3), 3.0–3.9 (m, 4), 4.5–5.1 (br s, 1), 7.1–7.9 ppm (m, 12).

*Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.16; H, 6.46; N, 9.15.

**1-Benzoyl-4-formyl-4-methyl-5-phenyl-1,4-dihydropyridazine (6b).**—To 500 mg (1.31 mmol) of the aldehyde **5b** dissolved in 30 ml of $CH_2Cl_2$ was added 300 mg of *N*-bromosuccinimide in 8.0 ml of pyridine. After the solution had stood for 6 hr at room temperature, 16.5 ml of iced, concentrated HCl was added and the organic phase was washed, dried, and evaporated. Addition of ether and chilling gave 380 mg (76%) of off-white crystals in two crops, mp (first crop) 111–113°. Recrystallization from methylene chloride–ether gave white crystals of **6b**: mp 113–114°; $\nu^{KBr}$ 1670, 1720 $cm^{-1}$; $\delta^{CDCl_3}$ 1.48 (s, 3), 6.52 (s, 1), 7.1–7.8 (m, 11), 7.85 ppm (s, 1).

*Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.09; H, 5.13; N, 9.12.

**1-Benzoyl-4-methyl-5-phenyl-1,4-dihydropyridazine (7b).**—To 200 mg (0.658 mmol) of **6b** dissolved in 20 ml of methanol was added 0.4 ml (0.7 mmol) of 10% potassium hydroxide. After the solution had stood for 20 min at 25°, 93 mg of white crystals of **7b** had precipitated from the solution. These crystals were collected and washed with cold methanol, mp 142–143°. The filtrate was neutralized with HCl, concentrated, and extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to an oil. Addition of ether gave 13 mg of 7b, mp 141–143°, total yield 106 mg (58%). Recrystallization from ether–methylene chloride raised the melting point to 142.5–143°; $\nu^{KBr}$ 1650 $cm^{-1}$; $\delta^{CDCl_3}$ 1.26 (d, 3, $J$ = 7.0 Hz), 3.55 (q of d, 1, $J_{4,4-CH_3}$ = 7.0, $J_{3,4}$ = 3.6 Hz), 6.95 (d, 1, $J$ = 3.6 Hz), 7.15–7.75 (m, 10), 7.90 ppm (s, 1).

*Anal.* Calcd for $C_{18}H_{15}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.05; H, 5.72; N, 10.18.

**Conversion of 6b to 4-Methyl-5-phenylpyridazine (9).**—To a solution of 100 mg (0.327 mmol) of the 4-formyl-1,4-dihydropyridazine **6b** in 30 ml of methanol was added 1.5 ml (2.7 mmol) of 10% KOH. After 1 hr at 25° the reaction mixture was neutralized with 1 *N* HCl. The methanol was then removed *in vacuo* under nitrogen, chloroform was added to the remaining oil, and this solution was washed with $NaHCO_3$ and water and dried. The chloroform layer was evaporated under $N_2$. An nmr spectrum ($CDCl_3$) indicated equal amounts of 4-methyl-5-phenylpyridazine (**9**) [$\delta^{CDCl_3}$ 2.28 (s, 3), 7.05–7.55 (m), 8.95 (s, 1), 9.02 (s, 1)] and 4-methyl-5-phenyl-1,4-dihydropyridazine (**8**) [$\delta^{CDCl_3}$ 1.03 (d, 3, $J$ = 6.8 Hz), 3.3–3.6 (m, 1), 6.62 (d, 1, $J$ = 4 Hz)]. Oxygen was then bubbled through the solution for 15 min. An nmr spectrum of the black solution showed mostly 4-methyl-5-phenylpyridazine with some of the dihydro compound **8** remaining. After 45 min of oxygenation the nmr showed only 4-methyl-5-phenylpyridazine and a few impurity peaks. The solution was then evaporated and the residue was distilled in a short-path sublimer at 73°. The distillate crystallized on the cold finger upon the addition of a seed crystal of authentic 4-methyl-5-phenylpyridazine. The sublimation was continued and gave 25 mg (45%) of colorless crystals, mp 80–82° (lit.[9] 82–84°). Resublimation raised the melting point to 82–83°. The infrared spectrum was identical with a spectrum of authentic 4-methyl-5-phenylpyridazine.

**Competition of Thermal and Acid-Catalyzed Reactions of 3b.**—Alcohol **3b** (31 mg) and 11 or 22 mg of benzoic acid were dissolved in 1 ml of benzene and placed in a test tube with a 6-cm glass rod sealed to the bottom as a stem. The solution was frozen in an ice–salt bath and the tube was sealed and supported on the stem above the liquid level of a refluxing solvent (toluene, benzene, or acetone). After 18 hr (72 hr with acetone bath) the tubes were opened, benzene was evaporated, and nmr spectra were taken in $CDCl_3$. The composition of the mixtures were determined by integration of the methyl region of these spectra, which generally contained three peaks: δ 2.15 (oxide **2b**), 1.20 (aldehyde **5b**), and 1.30 (unknown, usually less than 10% of the total integral).

| | | % of total methyl | |
|---|---|---|---|
| Temp, °C | Acid, mg | 2b | 5b |
| 110 | 11 | 55 | 35 |
| 80 | 11 | 90 | 5 |
| 80 | 22 | 90 | |
| 56 | 11 | 80 | |

**Registry No.**—**1**, 5109-67-1; **2b**, 36529-44-9; **3b**, 36529-45-0; **3b** benzoate, 36529-46-1; **3b** acetate, 36529-47-2; **4b**, 36529-55-2; **5a**, 36529-56-3; **5a**, 1,2-diacetyl derivative, 36529-57-4; **5b**, 36529-58-5; **5b**, 36529-58-5; **5b** 1,2-bibenzoyl derivative, 36529-59-6; **6b**, 36529-60-9; **7b**, 36529-61-0; 1-benzoyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazine-4-methanol, 36529-62-1.

# Heterocyclic Studies. 38. Rearrangement of a 9-Acyl-1,9-diazabicyclo[4.2.1]nonadienone to a Pyrrolo[1,2-*b*]pyridazinone[1]

JAMES A. MOORE,* RICHARD C. GEARHART, OTIS S. ROTHENBERGER, PATRICIA C. THORSTENSON, AND ROBERT H. WOOD

*Department of Chemistry, University of Delaware, Newark, Delaware 19711*

*Received July 17, 1972*

Rearrangement of the diazabicyclo[4.2.0] ketone **1** by the action of heat, acid, or base gives the pyrrolopyridazinone **2** plus formaldehyde. The structure of **2** was determined by X-ray crystallography.

We recently reported the formation of the adducts **1** by 1,3-dipolar cycloaddition of thermally generated 1-acyl-2,3-dihydro-1,2-diazepininium betaines and dimethyl acetylenedicarboxylate.[2] We now describe an unusual reaction of these adducts that occurs under a variety of conditions. The major product, obtained in 90–100% yields in methanolic acid or base, or on heating in acetic acid or in a melt, are the pyrrolopyridazinones **2**. The remainder of the molecule, corresponding to $CH_2O$, was identified as formaldehyde.

**Structure of 2.**—The structure of **2a** was determined by X-ray crystal structure analysis. Figure 1 is a perspective view of the molecule from a point about 45° from the normal to the plane of the ring system. Hydrogen atoms are excluded for clarity. Bond distances and angles are given in Table I and II.[3]

The structure of the molecule in the crystal is such that the phenyl ring and nearest methoxy group are nearly perpendicular (89°) to the central ring system plane while the bromophenyl group is about 45° with

(1) Supported in part by Grant GP-9322 from the National Science Foundation.

(2) O. S. Rothenberger and J. A. Moore, *J. Org. Chem.*, **37**, 2796 (1972).

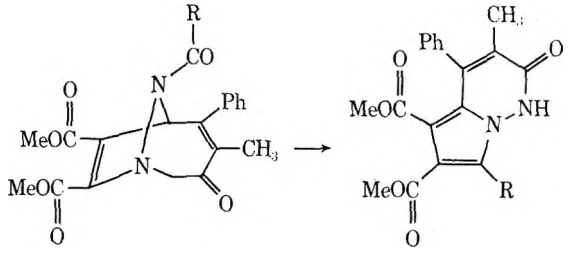
(3) Tables of fractional coordinates, thermal parameters, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-3774. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

TABLE I

INTERATOMIC BOND DISTANCES FOR NONHYDROGEN ATOMS AND THEIR ESTIMATED STANDARD DEVIATIONS FOR 2

| Atom 1 | Atom 2 | Distance, Å |
|---|---|---|
| Br | C74 | 1.909 (8) |
| C74 | C73 | 1.358 (10) |
| C73 | C72 | 1.390 (12) |
| C72 | C71 | 1.409 (10) |
| C71 | C76 | 1.361 (9) |
| C76 | C75 | 1.402 (11) |
| C75 | C74 | 1.377 (10) |
| C71 | C7 | 1.467 (11) |
| C7 | C6 | 1.393 (10) |
| C6 | C61 | 1.454 (12) |
| C61 | O611 | 1.182 (11) |
| C61 | O612 | 1.316 (11) |
| O612 | C62 | 1.421 (13) |
| C6 | C5 | 1.405 (11) |
| C5 | C51 | 1.479 (11) |
| C51 | O511 | 1.200 (10) |
| C51 | O512 | 1.335 (11) |
| O512 | C52 | 1.449 (11) |
| C5 | C4A | 1.369 (10) |
| C4A | C4 | 1.438 (12) |
| C4 | C41 | 1.489 (12) |
| C41 | C42 | 1.360 (16) |
| C42 | C43 | 1.387 (17) |
| C43 | C44 | 1.389 (20) |
| C44 | C45 | 1.317 (20)[a] |
| C45 | C46 | 1.393 (17) |
| C46 | C41 | 1.371 (15) |
| C4 | C3 | 1.348 (11) |
| C3 | C31 | 1.504 (12) |
| C3 | C2 | 1.433 (11) |
| C2 | O2 | 1.333 (9) |
| C2 | N1 | 1.303 (10) |
| N1 | N8 | 1.378 (8) |
| N8 | C7 | 1.375 (10) |

[a] This is shorter than the normal C–C bond distance in an aromatic ring; the difference is probably not significant.



**1a**, R = *p*-BrC$_6$H$_4$
**b**, R = C$_6$H$_5$
**c**, R = CH$_3$

**2** + CH$_2$=O

respect to the same plane. The central ring system is quite flat, the plane being defined by a least-squares fitting process using atoms C41, C4, C3, C31, C2, O2, N1, N8, C7, C71, C6, C61, C5, C51, and C4A; none of these defining atoms are more than 0.22 Å from the least-squares plane and all but three are within 0.1 Å of the defined plane. The molecules are tightly packed in parallel sheets with the plane of the central ring system roughly parallel with the 011 plane of the unit cells. The bond distances of the molecule agree favorably compared to those listed as typical bond lengths.[4] The bond lengths in the central ring system can be

(4) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.

TABLE II

INTERATOMIC BOND ANGLES AND THEIR ESTIMATED STANDARD DEVIATIONS FOR NONHYDROGEN ATOMS OF 2

| Atom 1 | Central atom | Atom 3 | Angle, deg |
|---|---|---|---|
| Br | C74 | C75 | 117.0 (5) |
| Br | C74 | C73 | 118.4 (6) |
| C73 | C74 | C75 | 124.6 (7) |
| C74 | C75 | C76 | 116.3 (6) |
| C75 | C76 | C71 | 122.4 (7) |
| C76 | C71 | C72 | 118.1 (7) |
| C71 | C72 | C73 | 121.3 (6) |
| C72 | C73 | C74 | 117.2 (7) |
| C7 | C71 | C76 | 121.7 (7) |
| C7 | C71 | C72 | 120.2 (6) |
| N8 | C7 | C71 | 123.7 (6) |
| N8 | C7 | C6 | 104.4 (7) |
| C71 | C7 | C6 | 131.7 (7) |
| C7 | C6 | C61 | 129.7 (7) |
| C6 | C61 | O611 | 124.5 (8) |
| C6 | C61 | O612 | 116.4 (7) |
| O611 | C61 | O612 | 118.6 (9) |
| C61 | O612 | C62 | 118.9 (7) |
| C7 | C6 | C5 | 109.7 (6) |
| C61 | C6 | C5 | 120.1 (7) |
| C6 | C5 | C51 | 126.1 (6) |
| C6 | C5 | C4A | 107.4 (7) |
| C51 | C5 | C4A | 126.5 (7) |
| C5 | C51 | O511 | 127.1 (8) |
| C5 | C51 | O512 | 111.1 (7) |
| O511 | C51 | O512 | 121.8 (7) |
| C51 | O512 | C52 | 116.0 (6) |
| C5 | C4A | C4 | 136.8 (7) |
| C5 | C4A | N8 | 106.8 (7) |
| N8 | C4A | C4 | 116.4 (6) |
| C4A | C4 | C41 | 117.3 (7) |
| C41 | C42 | C43 | 122.4 (10) |
| C42 | C43 | C44 | 116.9 (11) |
| C43 | C44 | C45 | 121.7 (12) |
| C44 | C45 | C46 | 120.8 (11) |
| C45 | C46 | C41 | 119.6 (10) |
| C41 | C4 | C3 | 123.5 (8) |
| C4A | C4 | C3 | 119.2 (7) |
| C4 | C3 | C31 | 123.2 (7) |
| C4 | C3 | C2 | 118.4 (7) |
| C31 | C3 | C2 | 118.5 (7) |
| C3 | C2 | O2 | 118.7 (7) |
| C3 | C2 | N1 | 125.6 (7) |
| O2 | C2 | N1 | 115.7 (6) |
| C2 | N1 | N8 | 114.6 (6) |
| N1 | N8 | C4A | 125.8 (6) |
| N1 | N8 | C7 | 122.4 (6) |
| C4A | N8 | C7 | 111.7 (6) |

seen to have intermediate values consistent with a 10-$\pi$ aromatic system.

**On the Formation of 2.**—When the reaction of **1** (R = BrC$_6$H$_4$) was carried out in acetic acid-$d_4$, two singlet peaks of equal intensity ($\delta$ 4.8 and 5.2, total integral 2 with respect to the CH$_3$ singlet) were present in the nmr spectrum of the total reaction mixture in addition to the peaks due to **2**. Similar peaks were present in the spectrum of a solution prepared from gaseous CH$_2$O and glacial acetic acid. When the amount of CH$_2$O was increased substantially, the intensity of the singlet at $\delta$ 4.8 increased relative to that at $\delta$ 5.2, and the $\delta$ 4.9 peak became a doublet ($J$ = 2 Hz). The species giving rise to these nmr signals are not known with certainty. No stable compounds such as methylene glycol diacetate are known to be

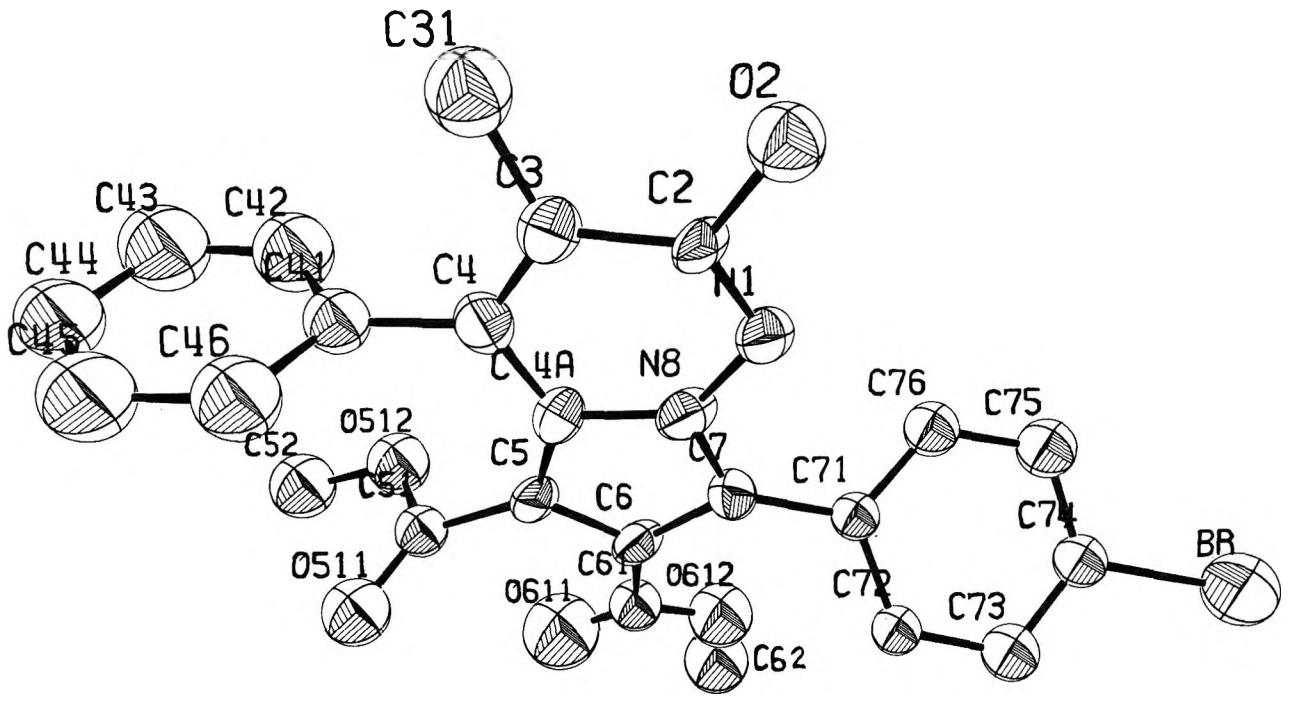
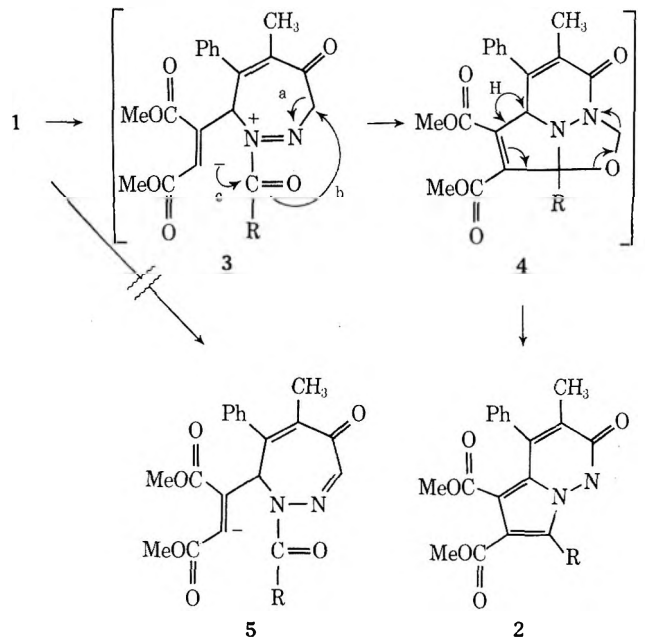


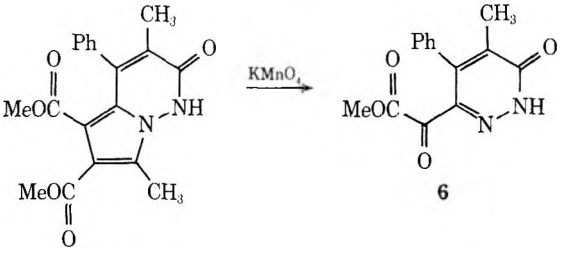

Figure 1.—ORTEP drawing of 2 in perspective with 50% probability thermal ellipsoids (hydrogens are not shown).

formed in $HCHO-CH_3CO_2H$ solutions.[5] We presume that at low HCHO concentration, the nmr spectrum is due to $CH_3CO_2CH_2OCH_2OH$; at higher concentrations the spectrum may arise from a mixture of this dimethylene glycol monoacetate plus paraldehyde, or from $CH_3CO_2CH_2(OCH_2)_nOH$.

The presence of $CH_2O$ in the reaction mixture of **1** in acetic acid-$d_4$ is significant, since it reveals that no deuterium exchange occurs in the $CH_2$ group. The conversion of **1** to **2** must involve breaking the N1–C8 bond at some point; the fact that the $CH_2$ unit remains intact means that at least in acetic acid, this step does not occur by $\beta$ elimination to **5**. Overall, the reaction appears to include the bond changes a, b, and c depicted in **3**. The timing of these steps cannot be specified, and the intermediates **3** and **4** represent an arbitrary formalism at this point.

The 10-$\pi$ aromatic pyrrolo[1,2-*b*]pyridazine system of **2** has been encountered before in a cycloaddition of dimethyl acetylenedicarboxylate and pyridazine.[6] The tautomeric structure **2** is consistent with the properties of the compound; it is a somewhat stronger acid [$pK_a$ (50% aqueous DMF) = 7.8] than the parent 3-pyridazinone [$pK_a$ ($H_2O$) = 10.4[7]]. The chemical properties of **2** were not extensively explored. The compounds are readily oxidized by $KMnO_4$. Very mild oxidation of **2c** (R = $CH_3$) gave a product, $C_{14}H_{12}N_2O_4$, in 40% yield. The composition and spectral properties [$\delta$ 2.07 (s, 3), 3.85 (s, 3), 12.9 (s, 1); $\nu$ 1760, 1720, 1660 $cm^{-1}$] indicate the glyoxylate structure **6**,




apparently formed by fortuitously incomplete oxidation under the conditions used. Comparable $KMnO_4$ oxidation to an oxalate product has been reported in other systems.[8]

## Experimental Section

**7,8-Bis(methoxycarbonyl)-9-*p*-bromobenzoyl-4-methyl-5-phenyl-1,9-diazabicyclo[4.2.1]nona-4,7-dien-3-one (1a).**—A suspension of 2.0 g (5.2 mmol) of 2-*p*-bromobenzoyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one[9] in 20 ml of

(5) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold, New York, N. Y., 1964, p 345.

(6) R. L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 764 (1956).

(7) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(8) E. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967).

(9) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

freshly distilled dimethyl acetylenedicarboxylate was heated at 80° for 8 hr. A homogeneous solution resulted after 15 min. After 8 hr the total reaction mixture was chromatographed (silicic acid, $CNCl_3$) to give a pale yellow oil. Crystallization from ether gave 966 mg (32%) of white, crystalline **1a**: mp 181°; $\nu^{KBr}$ 1750, 1720, 1650, 1620 $cm^{-1}$; $\delta^{CDCl_3}$ 1.92 (d, $J$ = 1 Hz, 3), 3.43 (s, 3), 3.72 (s, 3), 5.00 (q, $J$ = 1 Hz, H-6), 5.39 (d, $J$ = 4.5 Hz), 5.63 (d, $J$ = 4.5 Hz), 7.13–7.68 (m, 9).

*Anal.* Calcd for $C_{25}H_{21}N_2O_6Br$: C, 57.15; H, 4.03. Found: C, 56.85; H, 3.84.

**5,6-Bis(methoxycarbonyl)-7-*p*-bromophenyl-3-methyl-4-phenylpyrrolo[1,2-*b*]pyridazin-2-one (2a). A. Methanolic Sodium Methoxide.**—A 570-mg (1.1 mmol) sample of **1a** was added to a solution of 25 ml of anhydrous methanol containing 0.2 g of sodium methoxide. After slight warming to dissolve **1a** the solution was kept at 25° for 30 min and was then neutralized by the dropwise addition of concentrated HCl. Removal of methanol under vacuum left a solid white residue, which was taken up in $CH_2Cl_2$. After washing ($H_2O$), drying ($MgSO_4$), and removal of solvent, there remained a pale yellow solid which was recrystallized from methanol to give 525 mg (97%) of **2a** as fine white needles: mp 262°; $\nu^{KBr}$ 1700, 1610 $cm^{-1}$; $\delta^{CDCl_3}$ 1.87 (s, 3), 3.22 (s, 3), 3.63 (s, 3), 7.2–7.7 (m, 10). Slow crystallization from ethanol gave the alcoholate.

*Anal.* Calcd for $C_{24}H_{19}N_2O_5Br$: C, 57.77; H, 4.63; N, 5.19. Found: C, 57.79; H, 4.30; N, 5.11.

Crystallization from 2-propanol also produced an alcoholate.

Crystals suitable for X-ray analysis were obtained by slowly cooling a hot, saturated solution of **2a** in benzene to 40° during 6 hr and maintaining this temperature for 2 days. This procedure gave very pale yellow cubes whose melting point and ir spectrum were identical with those of a sample crystallized from methanol.

*Anal.* Calcd for $C_{24}H_{19}N_2O_5Br$: C, 58.19; H, 3.87; *m/e* 494.0478. Found: C, 58.28; H, 3.80; *m/e* 494.0489.

**B. Pyrolysis in Melt.**—A 105-mg (0.2 mmol) sample of **1a** was heated at 195° in a test tube for 15 min. The smell of formaldehyde was readily apparent. Crystals of **2a** began to form in the liquid melt after 5 min of heating. When the odor of formaldehyde was no longer detectable, the sample was cooled and weighed (98 mg, 99%). Recrystallization from methanol gave **2a**, mp 260–261°; the melting point was unchanged on admixture with **2a** prepared in part A above. In another experiment, the gaseous formaldehyde was led into an ethanol solution of dimedone. Colorless crystals of the methylene bisdione crystallized, mp 189–190° (lit.[10] mp 191–191.5).

**C. Acetic Acid.**—A solution of 20 mg (0.05 mmol) of **1a** in 0.5 ml of acetic acid-$d_4$ was heated in an nmr tube at 100°. After 10 min the nmr spectrum indicated a 1:1 mixture of unreacted **1a** and product **2a**. In addition to the signals assignable to **1a** and **2a**, the spectrum contained two singlets of equal intensity at $\delta$ 4.8 and 5.2. The nmr spectrum after 30 min at 100° showed complete conversion of **1a** to **2a**. The two singlets at $\delta$ 4.8 and 5.2 had a total integral of 2 with respect to the $CH_3$ singlet of **2a**. Upon cooling, pale yellow crystals formed; the mp and ir spectrum were identical with those of **2a** obtained previously. The conversion of **1a** to **2a** in hot acetic acid proceeded in 90% yield on a preparative scale (200 mg of **1a**).

The nmr spectrum of gaseous formaldehyde (generated thermally from paraformaldehyde) in $CD_3CO_2D$ also exhibits two singlets of nearly equal intensity at $\delta$ 4.8 and 5.2. Incremental additions of gaseous formaldehyde increased the intensity of the upfield signal.

**D. Methanolic HCl.**—A solution of 50 mg (0.1 mmol) of **1a** in 10 ml of methanol and 1 ml of concentrated HCl was heated at 65° for 30 min. Removal of the solvents under reduced pressure and trituration of the oily residue with ether gave 45 mg of crystalline solid. The nmr spectrum of this material showed approximately 15% conversion of **1a** to **2a**. This mixture was redissolved in methanolic HCl and heated to reflux for 18 hr. Work-up as before gave pure **2a** (ir and nmr).

**5,6-Bis(methoxycarbonyl)-4,7-diphenyl-3-methylpyrrolo[1,2-*b*]pyridazin-2-one (2b).**—A solution of 250 mg (0.56 mmol) of **1b**[2] in 8 ml of methanol was treated with 2 ml of 50% sodium methoxide in methanol. After standing for 20 min at room temperature, the solution was acidified with concentrated HCl and reduced to an oil under reduced pressure. Addition of $CH_2Cl_2$ followed by washing ($H_2O$), drying ($MgSO_4$), and concentration gave a solid residue which was recrystallized from methanol to obtain 200 mg (86%) of **2b** as white needles: mp 230–231°; $\lambda_{max}^{MeOH}$ 238 nm ($\epsilon$ 26,900); p$K_a$ = 7.8 (67% DMF–$H_2O$); $\nu^{KBr}$ 3400, 1730, 1680, 1610 $cm^{-1}$; $\delta^{CDCl_3}$ 1.87 (s, 3), 3.24 (s, 3), 3.62 (s, 3), 7.43 (m, 10), 7.6–7.9 (b, 1).

*Anal.* Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.50; H, 4.72; N, 6.66.

The conversion of **1b** to **2b** was also effected in 84% yield (after recrystallization) by heating **1b** as a melt for 20 min at 170°.

**5,6-Bis(methoxycarbonyl)-3,7-dimethyl-4-phenylpyrrolo[1,2-*b*]pyridazin-2-one (2c).**—To a solution of 100 mg (0.26 mmol) of **1c**[2] in 3 ml of methanol was added 0.8 ml of 5% sodium methoxide in methanol. After standing for 5 min at room temperature, the solution was acidified and the product was isolated as described for **2b**; the oil crystallized from ether, giving 80 mg (87%) of **2c** as white crystals: mp 201–202°; $\lambda_{max}^{MeOH}$ 232 nm ($\epsilon$ 29,900); p$K_a$ = 7.7 (67% DMF–$H_2O$); $\nu^{KBr}$ 3240, 1710, 1680, 1620 $cm^{-1}$; $\delta^{CDCl_3}$ 1.97 (s, 3), 2.68 (s, 3), 3.23 (s, 3), 3.84 (s, 3), 7.42 (m, 5), 7.5–9.0 (b, 1).

*Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.16; H, 5.05; N, 7.73.

**Oxidation of 2 (R = $CH_3$).**—To a solution of 170 mg (0.48 mmol) of **2c** (R = $CH_3$) in 9 ml of water containing 6 drops of 6 *N* sodium hydroxide was added 500 mg of potassium permanganate. The resulting solution was stirred for 5 min and then acidified. Solid sodium bisulfite was added to reduce the excess manganese dioxide. The clear aqueous solution was extracted with $CH_2Cl_2$. Evaporation of the dried organic layer gave an oil which crystallized from ether to yield 60 mg (46%) of **methyl [(4-methyl-3-oxo-5-phenylpyridazinyl)-6]glyoxylate (6)** as white crystals: mp 194–195°; $\nu^{KBr}$ 3000–2700, 1760, 1720, 1660 $cm^{-1}$; $\delta^{CDCl_3}$ 2.07 (s, 3), 3.85 (s, 3), 7.42 (m, 5), 12.9 (s, 1).

*Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; O, 23.51. Found- C, 61.68; H, 4.70; O, 23.9.

**X-Ray Analysis.**—Crystals were received as prismatic needles; a sample showing good crystal quality under microscopic examination with and without polarized light was chosen from the batch. The sample was approximately 0.34 × 0.21 × 0.50 mm and was mounted with the 0.50-mm length parallel with the rotation axis of the goniometer head.

By preliminary precession camera investigation, the unit cell was found to be monoclinic. Data were taken on the sample in space group $P2_1/n$ because of the near-cubic form of the resulting cell. This space group has the general positions, $\pm(x, y, z; x + 1/2, y - 1/2, z + 1/2)$; the sample was thus mounted with its 101 axis parallel with the rotation axis of the goniometer.[11]

Precision lattice constants were obtained by least-squares refinement[11] of $2\theta$ diffractometer angular settings on 19 reflections in the range $5° < |2\theta| < 35°$ ($\lambda$ = 0.7107, for Mo $K_\alpha$ radiation). These calculations gave $a$ = 12.593 (2), $b$ = 14.429 (3), c = 12.441 (3), $\beta$ = 101.69° [$\cos\beta$ = −0.2026 (4)] (numbers in parentheses are the estimated standard deviation). Assuming four formula units per cell, the calculated density was found to be 1.486 (3) g/$cm^3$, which agrees favorably with the experimental density found by immersion in a liquid of equal density of 1.4 g/$cm^3$ at 21 ± 1°, the ambient laboratory temperature.

For Mo $K_\alpha$ radiation, the linear absorption coefficient, $\mu$, was calculated to be 19.4 $cm^{-1}$, which would cause no more than a 6% error in any structure factor calculation. Approximately 1600 independent reflections ($|\sin\theta/\lambda| \leq 0.649$ Å$^{-1}$) were measured by the $\theta$–$2\theta$ scanning technique using a card-controlled Picker diffractometer. With approximately 290 parameters to be set in the final anisotropic model (excluding hydrogens), this gives about five reflections per parameter to be set.

Diffracted intensities were measured at a take-off angle of approximately 2°. The range of each scan, at a rate of 2°/min, consisted of a reflection base width of 2° and an increment, $\Delta(2\theta) = (0.285 \tan\theta)°$, to allow for spectral dispersion; background counts, for 30-sec duration, were taken at limits of the scan. The intensities of three standard reflections were monitored at intervals of 50 data points as alignment checks while these three plus three others were used at roughly 12-hr intervals as decomposition checks. Through the data collection period, these monitored reflections showed no noticable trend. The criteria for distinguishing observed reflections from unobserved

(10) E. C. Horning, *J. Org. Chem.*, **11**, 95 (1946).

(11) All structure refinements were done using "X-ray 670" programs from Dr. James Stewart, University of Maryland. The Burroughs B-6700 computer at the University of Delaware was employed.

was set such that, to be observed, $F_{obsd} < 3.0\sigma_F$, where $\sigma_F$ is the standard deviation on $F_{obsd}$ computed from scan and background counts corrected for instrumental instability (estimated as 0.5%).

The structure was resolved through an initial three-dimensional Patterson synthesis, which gave the position of the bromine atom. Successive three-dimensional Fourier and difference-Fourier syntheses quickly lead to the placement of all other nonhydrogen atoms.

All nonhydrogen atoms were then treated with converging cycles of full-matrix least-squares refinement. In the final cycles, hydrogen positions were calculated,[12] nonunit weights were introduced, and anisotropic temperature factors were introduced for all nonhydrogen atoms. Hydrogen positional and thermal parameters were not refined but positional parameters were recalculated at the close of each least squares cycle to reposition them according to shifts in the nonhydrogen ring and methyl carbon atoms. Hydrogens were placed at 1.08 Å from the nearest phenyl-ring atoms and in the plane of the rings, at 0.99 Å from the nitrogen, N1, at approximately 109° from the two next nearest ring atoms (C2 and N8), and at 1.10 Å from the three terminal methyl carbons, C52, C62, and C31, at the proper tetrahedral angles (bonding distances are from ref 4). The phenyl-ring and nitrogen hydrogen positions checked satisfactorily against their respective positions on difference Fourier maps. It was not possible to locate hydrogens about the three methyl carbons on difference maps, possibly owing to relatively free rotation of these methyl groups.

The weighting function used in the final least-squares cycles was $w = 1/|\Delta\bar{F}|^2$, where $|\Delta\bar{F}| = A + B|\bar{F}_{obsd}|$, and $A$ and $B$ are obtained from a plot of $\Delta\bar{F}$ *vs.* $|\bar{F}_{obsd}|$ for 20 groups of reflections, each group containing about the same number of reflections. The plot was linear and gave values of 2.80 and 0.0492 for $A$ and $B$, respectively.

The last cycle yielded a conventional $R$ value of 0.052 and a weighted residual, $wR = 0.068$. Because the primary interest of this study was in the overall architecture of the molecule rather than in the structural details of bond lengths, angles, and thermal parameters, costly additional refinement computations were not made. A final difference Fourier synthesis having a maximum electron density of 1 e/Å$^3$ was judged to be free of significant features.

(12) Hydrogen positional parameters were calculated with ATMCAL, adapted from a general hydrogen position calculating program supplied by Dr. Lloyd Guggenberger, The Du Pont Co., Wilmington, Del.

**Registry No.**—**1a**, 36434-07-8; **1b**, 36004-93-0; **1c**, 36004-92-9; **2a**, 36411-13-9; **2b**, 36411-14-0; **2c**, 36411-15-1; **6**, 36411-16-2.

# The Synthesis of 2-Aza-6-oxaadamantane

Y. KASHMAN* AND E. BENARY

*Department of Chemistry, Tel-Aviv University, Ramat-Aviv, Israel*

*Received May 19, 1972*

A new synthesis of 2-aza-6-oxaadamantane from suitably substituted 9-azabicyclo[3.3.1]nonane (prepared by a double Michael addition of a primary amine to 2,7-cyclooctadienone), has been achieved. The nmr of the various azabicyclic compounds were investigated; $J$ values of the ketones and $T_c$ values of the $N$-acetyl compounds are discussed.

The 2-aza-6-oxaadamantanic skeleton has already been synthesized by another method.[1] In this paper we report a new approach which should enable the introduction of other functional groups. This method is analogous to that used in the preparation of 2-oxa-[2] and 2-phospha-6-oxaadamantanes.[3]

2-Acetyl-2-aza-6-oxaadamantane was prepared by the steps shown in Scheme I. The parent material in the synthesis, 9-benzyl-9-azabicyclo[3.3.1]nonan-3-one (**1**),[4] was prepared by the exothermic addition of benzylamine to cyclooctadienone, as was also found by Bottini;[5] consecutive reduction of **1** by $LiAlH_4$ yielded the expected endo alcohol **2**,[6] from which the benzyl group could be cleaved by hydrogenolysis under acidic conditions to yield *endo*-9-azabicyclo[3.3.1]nonan-3-ol (**3**) (milder hydrogenation conditions; *e.g.*, hydrogenation in ethanol, at room temperature and 60 psi did not affect the benzyl group). Compound **3** which is a hygroscopic material was identical in all respects with the one described in the literature.[7] Attempts to produce the 9-azabicyclo[3.3.1]nonan-3-one directly by addition of ammonia to cyclooctadienone failed; the only product which was isolated, in ~50% from the reaction mixture, seems to be 3,7-bis[9-(9-azabicyclo[3.3.1]-nonan-3-one)]cyclooctanone (**4**).

Treatment of compound **3** with acetic anhydride–pyridine acetylated the amine as well as the hydroxy group to yield *endo*-9-azabicyclo[3.3.1]nonan-3-ol (**5**) which, on mild basic hydrolysis gave the corresponding alcohol (**6**).[7] (Schotten–Baumann acetylation of **2** which should result in **6** in one step, gave much lower yields due to side reactions.)

Treatment of the endo alcohol **6** with lead tetraacetate in boiling benzene,[2,3] or better in the presence of $Pb(OAc)_4$ and iodine,[8] gave two compounds. Chromatographic separation gave the desired 2-acetyl-2-aza-6-oxaadamantane (**7**) and the parent ketone, 9-acetyl-9-azabicyclo[3.3.1]nonan-3-one (**8**). The formation of **7** from **6** confirms the endo configuration of the latter, since epimerization is not expected to occur in these radical oxidation procedures.[2] Of interest was the nmr spectrum of **7** recorded at 100° (in hexachlorobutadiene), above its coalescence temperature (*vide infra*), which indicated the higher symmetry of the compound in comparison to the spectrum at room temperature. A double irradiation experiment, carried out under these conditions, enabled the measurement of various $J$ values of the system.

Although oxidation of tertiary amines by $Pb(OAc)_4$

(1) H. Stetter, *Justus Liebigs Ann. Chem.*, **709**, 170 (1967).

(2) M. Fisch, S. Smallcombe, J. C. Gramain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970).

(3) Y. Kashman and E. Benary, *Tetrahedron*, in press.

(4) G. F. Boehringer, Belgian Patent 623889 (1963). *Chem. Abstr.*, **60**, 13285*h* (1964).

(5) A. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971).

(6) (a) K. Stach and O. Dold, *Arzneimittel Frosch.*, **13**, 1015 (1963); (b) H. O. House, H. C. Müller, C. G. Piff, and P. P. Wickhaum, *J. Org. Chem.*, **28**, 2407 (1963).

(7) K. Alder and H. A. Dortman, *Chem. Ber.*, **86**, 1544 (1953).

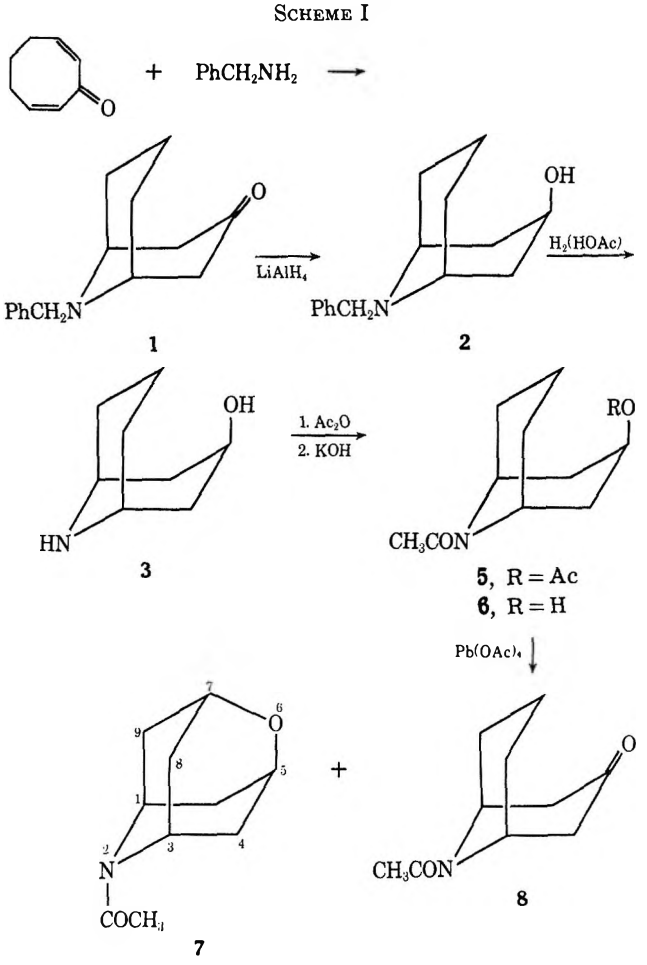
(8) (a) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964); (b) M. L. Mihailovic, Z. Cekovic, V. Andrevic, R. Matic, and D. Jeremie, *Tetrahedron*, **24**, 4947 (1968); (c) W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1964); (d) T. Mori, K. Matsui, and H. Nozaki, *Bull. Chem. Soc. Jap.*, **43**, 231 (1970).

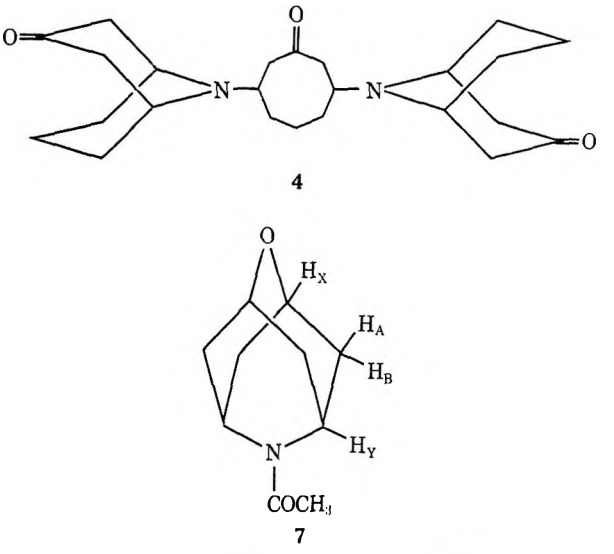
TABLE I

| Compd | $H_1,H_5$ | $H_2,H_4,H_2',H_4'$ | 2 $H_6$, 2 $H_7$, 2 $H_8$ | Aromatic protons | Other protons | Solvent |
|---|---|---|---|---|---|---|
| 1 | 3.25–3.40 | 2.71 (dd)[a]<br>2.22 (dd) | 1.34–2.67 | 7.18–7.48 | 3.88 (s, $PhCH_2$) | *b* |
| 2 | 2.90–3.14 | 1.00–2.56 | 1.00–2.56 | 7.00–7.50 | 3.86 (s, $PhCH_2$)<br>4.23 (m, C-3 H) | *b* |
| 3 | 2.88–3.12 | 1.64–2.82 | 1.64–2.82 | | 3.26 (m, C-3 H) | *c* |
| 5 | 3.98–4.24 (1 H)<br>4.80–5.10 (1 H) | 1.40–2.50 | 1.40–2.50 | | 4.86 (m, C-3 H)<br>2.03 (s, $NCOCH_3$)<br>2.06 (s, $OCOCH_3$) | *b* |
| 6 | 3.94–4.26 (1 H)<br>4.78–5.10 (1 H) | 1.40–2.50 | 1.40–2.50 | | 3.62 (m, C-3 H)<br>2.03 (s, $NCOCH_3$) | *b* |
| 8 | 4.30–4.50 (1 H)<br>5.10–5.30 (1 H) | 2.63 (dd)[a]<br>2.36 (dd) | 1.30–1.90 | | 2.16 (s, $NCOCH_3$) | *b* |
| 9 | 4.30–4.52 | 2.66 (dd)[a]<br>2.36 (dd) | 1.44–2.14 | 6.70–7.40 | | *b* |
| 10 | 4.05–4.30 | 1.24–2.67 | 1.24–2.67 | 6.50–7.40 | 3.78 (m, C-3 H) | *b* |
| 11 | 4.20–4.90 | 1.30–2.90 | 1.30–2.90 | 7.00–7.60 | | *d* |
| 12 | 3.50–3.70 | 2.65 (dd)[a]<br>2.38 (dd) | 1.44–2.00 | | | *b* |

[a] For $J$ values see Table II. [b] In $CDCl_3$. [c] In $D_2O$. [d] In hexachlorobutadiene.

SCHEME I




$\delta_A$ 1.90 (dd, $J_{AB}$ = 4, $J_{AX}$ = 4, $J_{AY} \simeq$ 1 Hz)
$\delta_B$ 1.57 (dd, $J_{AB}$ = 13, $J_{BY}$ = 4, $J_{BX}$ = 1.5 Hz)

is possible (benzyl amines are known to yield the corresponding benzamides),[9] attempts were made to prepare the oxaazaadamantane system by ring closure of compound **2**; however, no unequivocally characterized compound could be isolated from these experiments. Furthermore, even when the weakly basic arylamine **10** (*endo*-9-phenyl-9-azabicyclo[3.3.1]nonan-3-ol) was used, no identifiable compound could be isolated from the various reaction mixtures. Amine **10** was prepared by a route analogous to that used for **2**, although it has been previously synthesized by the Robinson and Scöpff reaction.[10]

The nmr spectra of **1**–**6** and **8**–**12** appear in Table I.

Examination of the nmr spectra of the various 9-aza ketones (Table II) reveals that, in all the cases, the C-2 (C-4) geminal protons are coupled to different extents with the C-1 (C-5) protons.[11] The distorted chair which has already been suggested by Le Fevre[12] for $\psi$-pelletierine is in accord with the measured $J$ values found in our measurements, although the possibility of a chair–chair ↔ chair–boat equilibria[13] (of the piperidinic and piperidonic rings) cannot be cancelled out.

It was of interest to compare the above data with that of 9-phosphabicyclo[3.3.1]nonan-3-ones (**13**, **14**, and **15**).[3]

(9) J. B. Aylward, *Quart. Rev. Chem. Soc.*, **25**, 409 (1971), and references therein.

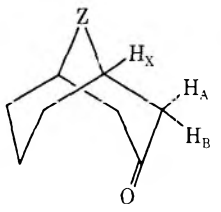
(10) G. F. Boehringer, German Patent 1174792 (1964), *Chem. Abstr.*, **61**, 10660 (1964).

(11) (a) N. S. Bhacca, and D. H. Williams, "Application of NMR Spectroscopy in Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 50; (b) E. Eliel and M. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(12) C. Y. Chen and R. J. W. LeFevre, *J. Chem. Soc. B* 539 (1966).

(13) M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 2847 (1971).

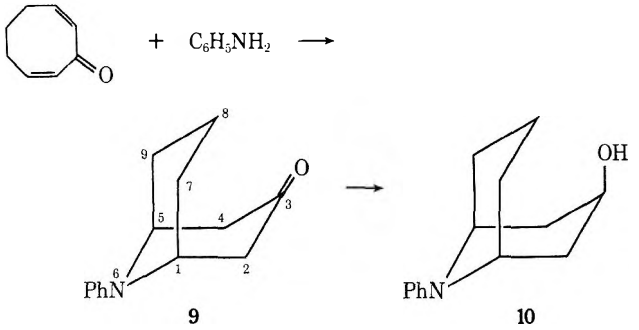
TABLE II



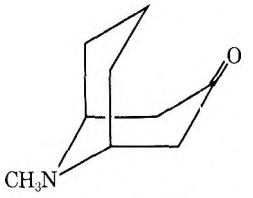

Z = N or P

| Compd | $H_A$ ($H_2$,$H_4$) | $H_B$ ($H_2$,$H_4$) | $H_X$ ($H_1$,$H_5$) | $J_{H_A,H_B}$ | $J_{H_A,H_X}$ | $J_{H_B,H_X}$ |
|---|---|---|---|---|---|---|
| ψ-Pelletierine[a] | 2.82 | 2.00 | 3.30 | 16.2 | 6.6 | 1 |
| 9 | 2.66 | 2.36 | 4.47 | 16 | 6 | 1 |
| 1 | 2.71 | 2.22 | 3.32 | 16 | 7 | 1 |
| 8 | 2.63 | 2.36 | 4.42<br>5.20 | 16 | 6 | 1.5 |
| 11 | 2.49 | 2.10 | 4.55 | 16 | 6 | 1.5 |
| 13[b] | 3.40 | 2.5–3.0 | 2.5–3.0 | 18 | 4 | |
| 14[b] | 3.52 | 2.85 | 2.7 | 18 | 4 | 1 |
| 15[b] | 3.26 | 2.60 | 2.2–2.5 | 18 | 4 | 1 |

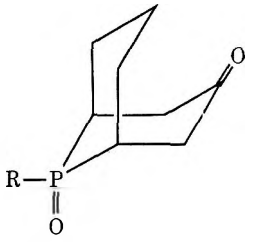
[a] Reference 12. [b] The nmr spectrum was recorded on a JEOL 60-Mc instrument with simultaneous irradiation of the P atom.




**9** **10**




ψ-Pelletierine




**13**, R = Ph
**14**, R = $C_6H_{11}$
**15**, R = $PhCH_2$

The almost equal $J$ values (Table II) found in both series seems to indicate a similar distortion of the phosphorinanonic ring compared with the piperidonic one, with the exception that in the former the preference of the distorted chair over the distorted boat seems to us more likely, because of additional interactions in the latter conformer between the axial ligand on the phosphorus and the carbonyl group.

In conclusion, it is seen that the phosphorus atom, compared with the nitrogen, does not change to any large extent the conformations of the phospha bicyclic compounds.

The activation energy of the well-known restricted rotation around the C–N bond in amides[14] depends, in the case of compound **7**, on the difference between the planar ground state in which C-1, N, C-3, and $COCH_3$ are all in the same plane, and the transition state, in which the $COCH_3$ group is perpendicular to the C-1, N, and C-3 plane. The $\Delta G^*$ value (17.5 kcal/mol)[15] calculated using the expression $\Delta G^* = RT(\ln kT/h - \ln \pi\Delta\nu/\sqrt{2})$[18] ($\Delta\nu = 0.85$, $T_c = 80°$) is similar to the value found for dimethylacetamide,[19] indicating thereby that a similar barrier of rotation exist in **7** as well as in the open-chain amide.

Activation energies for **5**, **6**, and **8** cannot be easily calculated from the $T_c$ values (106, 110, and 86°, respectively) because of their conformational mobility; nevertheless it was interesting to find a similar $T_c$ value for compounds **8** and **7**,[20] while for compounds **5** and **6** the value is higher by 20–30° (for similar $\Delta\nu$ values). This last enhancement may originate from a larger contribution of the chair–boat conformation,[21] upon which the C-3 proton comes into a "flag pole interaction" with the acetyl group in the transition state (in which the $COCH_3$ is perpendicular to the C-1, N, and C-3 plane). Other derivatives of these azabicyclo[3.3.1]-nonanes are now under investigation for nmr study.

## Experimental Section

Melting-points were taken on a Unimelt Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord Model 337 spectrophotometer. Nmr spectra were taken either on a Varian HA-100 spectrometer or a JEOL JNM-C-60HL spectrometer, 5–10% solution in $CDCl_3$ (unless otherwise indicated), containing TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU 6 instrument.

**9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one** (**1**).—To a solution of 2,7-cyclooctadien-1-one (10 g) in methanol (50 ml) was added slowly while swirling at 0° benzylamine (10 g), and the mixture was allowed to stand at room temperature until no more dienone could be detected by gc, tlc, or ir. The product which crystallized out from the reaction mixture (16.5 g) was recrystallized from methanol–hexane, mp 72° (lit.[4] 70–73°).

*endo*-**9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol** (**2**).—To a suspension of $LiAlH_4$ (1 g) in dry ether (80 ml) a solution of **1** (5 g) in ether (100 ml) was added dropwise, and the mixture was then heated at reflux with stirring for 2 hr. After this cooled the excess reagent was decomposed by EtOAc and a saturated solution of $Na_2SO_4$ was added. The solution was filtered, dried ($Na_2SO_4$), and evaporated. Recrystallization from benzene–hexane gave 4.7 g, mp 69° (in the literature[6] it is not given).

(14) (a) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 517 (1970); (b) P. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).

(15) As the $\Delta G^*$ expression is only strictly applicable to the coalescence of two sharp singlets, a value of ~0.2 kcal/mol[16] should probably be added as was done in the case of 7-acetyl-7-azabicyclo[2.2.1]heptane.[17]

(16) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **89**, 760 (1967).

(17) R. F. Fraser and R. B. Swingle, *Can. J. Chem.*, **48**, 2065 (1970).

(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution NMR," McGraw-Hill, New York, N. Y., 1959, p 223.

(19) R. C. Newman and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968).

(20) Another compound which belongs to this group is the 9-benzoyl-9-azabicyclo[3.3.1]nonan-3-one (**11**) which was prepared in low yields by benzoylation of nor-ψ-pelletierine (**12**). In this compound the $\Delta G^*$ value is expected to be much lower than that in **8** mainly because (a) interaction between the phenyl and C=O reduces the energy of the transition state, (b) the ground state in **11** is of higher energy due to $A_{1,3}$ interactions between the *o*-phenyl protons and those at C-1 (C-5). Indeed the $\Delta G^*$ value calculated from the $T_c$ is only 14.8 kcal/mol.

(21) (a) W. A. C. Brown, C. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (b) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

*endo*-**9-Azabicyclo[3.3.1]nonan-3-ol** (**3**).—Compound **2** (2 g) dissolved in acetic acid (20 ml) was hydrogenated over 10% $PtO_2$ on charcoal at atmospheric pressure and room temperature for 12 hr. The product obtained following the usual work-up (1.1 gr) was crystallized from chloroform, mp 104° (lit.[7] 102–104°).

**3,7-Bis[9-(9-azabicyclo[3.3.1]nonan-3-one)]cyclooctanone** (**4**).—To a solution of 2,7-cyclooctadien-1-one (6 g) in methanol (20 ml) was added slowly while stirring a 10% $NH_3$ in MeOH solution (20 ml), and the mixture was allowed to stand at room temperature until no more dienone could be detected by ir. The methanol was concentrated and the residue filtered to give 3 g of **4**: mp 190° (acetone); ir $\nu_{max}^{KBr}$ 2920, 1700, 1280, 1225, 1200, 1150, 1115, 1055, 1010, 950, 845 $cm^{-1}$; nmr $\delta$ 3.60 (m, 4 H), 3.33 (m, 2 H), 2.10–3.00 (m, 12 H), 1.40–2.10 (m, 18 H); mass spectrum *m/e* (rel intensity) 400 (10), 382 (15), 262 (30), 242 (25), 218 (40), 178 (100). *Anal.* Calcd for $C_{24}H_{36}O_3N_2$: C, 71.96; H, 9.06; N, 6.99. Found: C, 72.20; H, 9.06; N, 6.57.

*endo*-**9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl Acetate** (**5**).—To a solution of compound **3** (1 g) in pyridine (10 ml) was added acetic anhydride (1 ml), and the solution was left at room temperature overnight. Following the usual work-up compound **5** (1.5 g) was obtained: mp 99–100° (hexane); ir $\nu_{max}^{CHCl_3}$ 1730, 1640, 1030, 800 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 222 (35, $M\cdot^+$), 210 (10), 182 (20), 166 (28), 165 (30), 124 (100). *Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 64.06; H, 8.50; N, 6.21. Found: C, 64.15; H, 8.48; N, 6.06.

*endo*-**9-Acetyl-9-azabicyclo[3.3.1]nonan-3-ol** (**6**).—Compound **5** (1 g) was left overnight in a 1% KOH–MeOH solution (20 ml). After neutralization by the addition of 10% HCl in MeOH solution (2 ml), the solvent was evaporated, the residue dissolved in chloroform, and the chloroform washed with water dried ($Na_2SO_4$) and evaporated. The white solid thus obtained was crystallized from hexane yielding **6** (700 mg): mp 128° (lit.[7] 128–129°); ir $\nu_{max}^{neat}$ 3320, 1600, 1020, 1050 $cm^{-1}$.

**2-Acetyl-2-aza-6-oxaadamantane** (**7**) **and 9-Acetyl-9-azabicyclo[3.3.1]nonan-3-one** (**8**).—A mixture of dry benzene (120 ml), lead tetraacetate (12 g, dried over $P_2O_5$ at 0.1 mm), and $CaCO_3$ (6 g, dried over $P_2O_5$) was heated for 15 min at reflux. Compound **6** (2 g) dissolved in benzene (100 ml) and iodine (5.2 g) was then added and refluxing was continued for 3 hr. The cooled solution was filtered and the filtrate washed with 10% aqueous $Na_2S_2O_3$ (30 ml) and water (15 ml). After the solution was dried and evaporated, the residue was chromatographed on a silica gel column. The first compound which was eluted with 3% MeOH–$CH_2Cl_2$ was compound **8** (500 mg): mp 115° (hexane); ir $\nu_{max}^{neat}$ 1630, 1185, 1100, 1050, 1020, 1000, 980, 950, 860, 780 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 181 (16, $M\cdot^+$), 153 (8), 138 (16), 124 (8), 96 (100). *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.39; N, 7.72. Found: C, 66.13; H, 8.29; N, 7.68. The second compound which was eluted with 5% MeOH–$CH_2Cl_2$ was **7** (700 mg): mp 86–87° (hexane); nmr $\delta$ 4.10–4.30 (1 H), 4.90–5.10 (1 H), 4.10–4.30 (2 H), 1.6–2.3 (8 H), 2.08 (s, $NCOCH_3$); ir $\nu_{max}^{neat}$ 1640, 1060, 1020, 1000, 970, 950, 860, 780 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 181 (100, $M\cdot^+$), 166 (5), 138 (30), 124 (35), 111 (50). *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.39; N, 7.72. Found: C, 66.20; H, 8.26; N, 8.85.

**9-Phenyl-9-azabicyclo[3.3.1]nonan-3-one** (**9**).—Following the same procedure as described for **1**, the addition of aniline (0.9 g) to 2,7-cyclooctadien-1-one (1.1 g) at 50° yielded compound **9** (1.2 g): bp 160–162° (0.1 mm); mp 70° (MeOH, lit.[10] 62–64°); ir $\nu_{max}^{KBr}$ 3605, 1700, 1600, 1115, 910, 740 $cm^{-1}$.

*endo*-**9-Phenyl-9-azabicyclo[3.3.1]nonan-3-ol** (**10**).—Reduction of compound **9** (1 g) under the same conditions as described for the reduction of **1** to give **2** yielded compound **10** (900 mg): mp 98° (benzene–hexane); ir $\nu_{max}^{KBr}$ 3220, 1600, 1060, 1025, 910, 730 $cm^{-1}$. *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.45; H, 8.90; N, 6.55.

**9-Azabicyclo[3.3.1]nonan-3-one** (**12**).—Compound **1** (1 g) dissolved in methanol (25 ml) was hydrogenated over 5% palladium on charcoal at room temperature and atmospheric pressure for 48 hr in the presence of calalylic amounts of $HClO_4$. After the usual work-up compound **12** (500 mg) was obtained, identical in all respects with the one described in the literature.[7]

**9-Benzoyl-9-azabicyclo[3.3.1]nonan-3-one** (**11**).—To a solution of **12** (150 mg) in pyridine (2 ml) freshly distilled benzoyl chloride (0.3 ml) was added at 0°. After 4 hr the reaction mixture was poured on ice water and worked up in the usual way. The crude product was chromatographed on an $Al_2O_3$ column to give compound **11** (80 mg): mp 84–85° (benzene-hexane); ir $\nu_{max}^{neat}$ 3030, 1710, 1630, 1600 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 243 (22, $M\cdot^+$), 138 (45, $C_8H_{12}NO\cdot^+$), 105 (100, $C_6H_5CO\cdot^+$).

**Registry No.**—**1**, 2291-58-9; **2**, 36079-66-0; **3**, 36079-67-1; **4**, 36146-86-8; **5**, 36079-68-2; **6**, 36079-69-3; **7**, 36146-87-9; **8**, 36146-88-0; **9**, 27092-81-5; **10**, 36079-70-6; **11**, 36146-90-4; **12**, 4390-39-0; 2-aza-6-oxaadamantane, 19557-29-0.

# Epimerization of *cis*-4-Amino-5-phenyl-3-isothiazolidinone 1,1-Dioxide and Its 4-*N*-Acetyl Derivative

JOHN CHARLES HOWARD

*Department of Cell and Molecular Biology, Medical College of Georgia, Augusta, Georgia 30902*

*Received June 23, 1972*

The synthesis of *cis*- and *trans*-4-amino-5-phenyl-3-isothiazolidinone 1,1-dioxide (**3** and **5**) *via* methanolysis of the corresponding 4-acetamido derivatives **1** and **6** and base-catalyzed ring closure is described. Both **1** and **3** undergo rapid and irreversible base-catalyzed epimerizations to **6** and **5**, respectively. These results require reversal of tentative configurational assignments for **1** and **6**.

Recently we reported the synthesis of *cis*- and *trans*-4-acetamido-5-phenyl-3-isothiazolidinone 1,1-dioxide (**1** and **6**) and their rearrangement to 4-benzylidene-2-methyl-2-oxazolin-5-one (**4**) in acetic anhydride–pyridine.[1] We now described the transformation of **1** and **6** to the corresponding 4-amino derivatives **3** and **5**; these are cyclic analogs of phenylalanine, and the first 4-amino-3-isothiazolidinone 1,1-dioxides to be isolated and characterized.[2] During this work it was found that **1** and **3** can be readily epimerized to **6** and **5**, respectively; this result requires reversal of our tentative configurational assignments for **1** and **6**.[3]

Methanolysis of **1** and **6** gave the corresponding 3-sulfamyl phenylalanine methyl esters **2** and **7**; the yield of **7** was consistently low, partly because the crude material was always contaminated with some of the *N*-acetyl derivative **9**, the initial methanolysis product.

(1) J. C. Howard, *J. Org. Chem.*, **36**, 1073 (1971).

(2) The synthesis of 4-amino-3-isothiazolidinone 1,1-dioxide has been reported, but it was characterized only as the silver salt and benzoyl derivative: H. Baganz and G. Dransch, *Chem. Ber.*, **93**, 784 (1960).

(3) These were assigned (ref 1) on the basis of their nmr coupling constants, $J_{4,5}$ = 10.6 (cis) and 7.7 Hz (trans) in pyridine-$d_5$, but with the caveat that such assignments were valid only in the absence of substituent electronegativity effects, which in the case of **1** and **6** are unknown. The new assignments are based on relative stabilities and are less subject to uncertainty.

TABLE I

RATE CONSTANTS FOR THE BASE-CATALYZED EPIMERIZATION OF 1 AND 3[a]

| Compd | Conen, $M \cdot 10^4$ | Base: Type | Base: Conen, $M$ | Temp, °C | $k_1$,[b] $sec^{-1} \cdot 10^2$ | $k_2$, $M^{-1}$ $sec^{-1}$ |
|---|---|---|---|---|---|---|
| 1 | 1.88 | $H_2O$–NaOH | 0.100 | 20.3 | 1.32 | 0.132 |
| 1 | 1.90 | $H_2O$–NaOH | 0.100 | 24.8 | 1.93 | 0.193 |
| 1 | 1.87 | $H_2O$–NaOH | 0.100 | 29.1 | 2.89 | 0.289 |
| 1 | 1.86 | $H_2O$–NaOH | 0.050 | 37.6 | 2.44 | 0.488 |
| 1 | 1.99 | $CH_3OH$–$CH_3ONa$ | 0.195 | 24.8 | 0.231 | 0.0118 |
| 3 | 1.835 | $H_2O$–NaOH | 0.200 | 20.3 | 0.376 | 0.0188 |
| 3 | 1.835 | $H_2O$–NaOH | 0.100 | 24.8 | 0.297 | 0.0297 |
| 3 | 1.835 | $H_2O$–NaOH | 0.150 | 24.8 | 0.468 | 0.0312 |
| 3 | 1.835 | $H_2O$–NaOH | 0.200 | 24.8 | 0.577 | 0.0289 |
| 3 | 1.835 | $H_2O$–NaOH | 0.250 | 24.8 | 0.741 | 0.0296 |
| 3 | 1.835 | $H_2O$–NaOH | 0.200 | 29.1 | 0.825 | 0.0413 |
| 3 | 1.790 | $H_2O$–NaOH | 0.100 | 37.6 | 0.774 | 0.0774 |

[a] All reaction mixtures except those in $CH_3OH$–$CH_3ONa$ were made up to ionic strength 1.00 with KCl. [b] Average of two runs, reproducibility ±3%. Activation parameters: **1**, $\Delta H^{\pm} = 13.1$ kcal $mol^{-1}$, $\Delta S^{\pm} = -18.0$ cal $mol^{-1}$ $deg^{-1}$; **3**, $\Delta H^{\pm} = 14.1$ kcal $mol^{-1}$, $\Delta S^{\pm} = -18.4$ cal $mol^{-1}$ $deg^{-1}$.

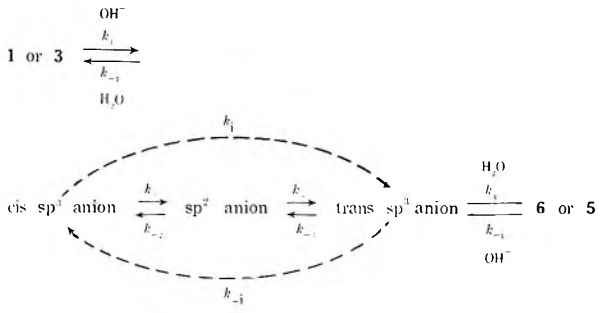
The ring closure reactions of **2**, **7**, and **9** proceeded rapidly with 1 equiv of sodium hydroxide to form in good yield **3**, **5**, and **6**, respectively.

The inner salt character of **3** and **5** was evidenced by their high decomposition points, insolubility in nonpolar solvents, infrared spectra (presence of $-NH_3^+$ and carboxylate bands), and titration data. The $pK_1$ (proton gained) was too low to be measured in water at the maximum solubility of **3**, but $pK_1'$ values of 2.00 and 2.29, respectively, were obtained for **3** and **5** in 50% ethanol. These are similar to the "proton lost" values of **1** (2.21) and **6** (2.47).[1] Under the same conditions saccharin (**8**), which has a similar acidic function, gave a $pK'$ value of 2.43. The $pK_2$ values of 5.86 and 6.16 for **3** and **5** reflect the large base-weakening effect of the sulfonyl group; for comparison, under the same conditions the $pK_2$ for phenylalanine was 9.16.

On one occasion the ring closure of **2** gave **5** instead of the expected **3**; this was found to be the effect of a slight excess of base. Further investigation revealed that in alkaline solution both **1** and **3** epimerized readily and irreversibly to **6** and **5**, respectively. We have investigated the kinetics of these two reactions at four temperatures and varying hydroxide ion concentrations. The rates were followed by recording the increase in absorbance which occurs at 223 nm during the reactions. The results (Table I) showed the epimerizations to be second order overall and first order with respect to substrate and hydroxide ion. The larger rate constant for the epimerization of **1** is considered to be a result of the electron-withdrawing capability of the *N*-acetyl group; the similar value of $\Delta S^{\pm}$ for **1** and **3** would appear to be inconsistent with a marked steric effect.

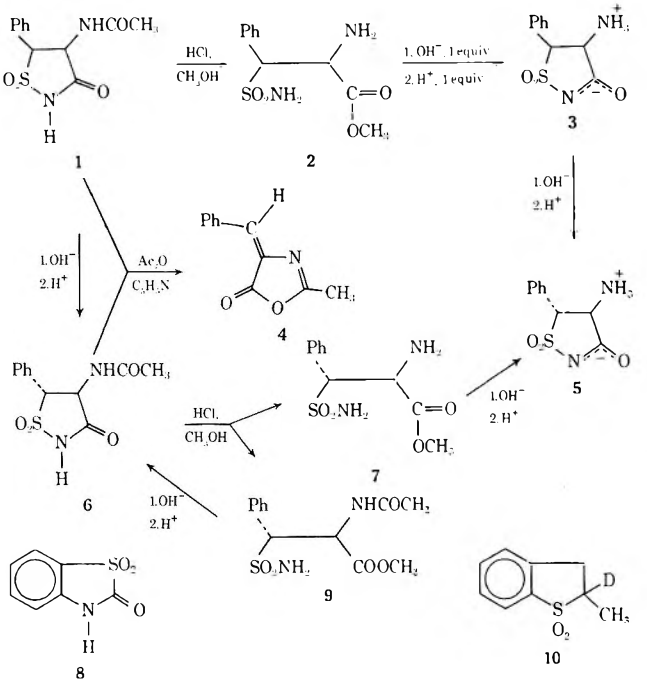
The driving force behind these epimerizations is almost certainly the release from crowding experienced by the α-sulfonyl carbanions[4] as they proceed from the cis to the less restrictive trans isomers. This may take place directly, by inversion of the cis $sp^3$ anion, or indirectly *via* formation of the $sp^2$ planar anion, which is then protonated exclusively from the side opposite to the original location of the proton.

Since α-sulfonyl carbanions are the conjugate bases




of very weak acids,[5] it can be assumed that $k_{-1}$ $[H_2O] \gg k_1$ $[OH^-]$ and $k_4$ $[H_2O] \gg k_{-4}$ $[OH^-]$. In addition, the observed irreversibility of the epimerizations requires that $k_i$ (or $k_2 + k_3$) be much larger than $k_{-i}$ (or $k_{-2} + k_{-3}$).

The large rate-accelerating effect of the phenyl group, previously noted for other α-sulfonyl systems,[6,7]




(4) For a discussion of α-sulfonyl carbanions see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 105–113, and ref 6–8.

(5) The $pK$ of dibenzyl sulfone is ~22: F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1957).

(6) F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *ibid.*, **90**, 426 (1968).

(7) L. A. Paquette, J. P. Freeman, and M. J. Wyvratt, *ibid.*, **93**, 3216 (1971).

becomes apparent when the 300-sec half-time for the epimerization of **1** in methanol–sodium methoxide (0.195 *M*) at 24.8° is compared with the 11.5 hr required for 64.6% racemization of the nonbenzylic α-sulfonyl carbanion from 2-deuterio-2-methyl-2,3-dihydrothiophene 1,1-dioxide (**10**) in methanol–sodium methoxide (0.16 *M*) at 76.2°.[8]

It would appear that **1** and **6**, since they are water soluble and differ strikingly from their epimers in uv and nmr absorbance, have distinct advantages as model compounds for the study of α-sulfonyl carbanions. At present we do not plan more experiments in this area.

## Experimental Section

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were taken on a calibrated Mel-Temp apparatus. The ir spectra were determined with a Perkin-Elmer 137-B spectrophotometer, and nmr spectra were determined by W. W. Simons of Sadtler Research Laboratories, Philadelphia, Pa., on a Varian A-60A spectrometer using TMS as an internal standard. Dissociation constants were measured at 24 ± 3° by methods previously described.[1]

**Rate Determinations.**—These were carried out in a Cary 14 spectrophotometer in thermostated cells (temperature variation ±0.05°). The reference cell contained the desired concentration of NaOH adjusted with KCl to constant ionic strength ($\mu$ = 1.00). The sample cell contained 2.60 ml of NaOH–KCl solution appropriately constituted to give the same hydroxide ion concentration and ionic strength as the reference cell at 2.80 ml total volume (in reactions carried out in methanol standard $CH_3ONa$ but no KCl was used). After thermal equilibration (20 min), 0.200 ml of stock solution ($2 \times 10^{-3}$ *M*) of **1** or **3** was added at zero time. The increase in absorbance at 223 nm was recorded for at least two and generally three half-times and the infinity absorbance was measured after ten half-times. Scans made at this time gave spectra identical with those of the products **6** or **5** under the same conditions. First-order constants were obtained from semilog plots of $A_\infty - A_t$ *vs* time and second-order constants by dividing these by the hydroxide ion concentration. Runs were made in duplicate, and excellent pseudo-first-order behavior was observed; rate constants were reproducible to within ±3%. Values for $E_{act}$ were calculated from the least-squares slopes of plots of log $k_2$ *vs.* $1/T$; $\Delta H^{\pm}$ and $\Delta S^{\pm}$ were calculated from $k_2$ and $E_{act}$ values by the usual equations.[9]

***threo*-3-Sulfamyl Phenylalanine Methyl Ester (2).**—Anhydrous HCl was added to 10 g (37 mmol) of *cis*-4-acetamido-5-phenyl-3-isothiazolidinone 1,1-dioxide[1] (**1**, previously identified[1] as trans) in 170 ml of methanol. After saturation the solution was refluxed for 3 hr and stored overnight at 25°. After chilling briefly, the precipitated hydrochloride salt was collected, washed with methanol–ether, dried at 25° (11 g), and stirred into 25 ml of 10% $Na_2CO_3$. The precipitate was collected, washed with water, and dried *in vacuo* at 25°, 6.5 g (59%), mp 156–157° dec; recrystallization from methanol raised the melting point to 158–160° dec; p*K* (proton gained) = 4.90; ir (mineral oil) 3350, 3200 ($-NH_2$), 1750 $cm^{-1}$ (s, C=O).

*Anal.* Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.46; H, 5.61; N, 10.70; S, 12.66.

***cis*-4-Amino-5-phenyl-3-isothiazolidinone 1,1-Dioxide (3).**—To 2.5 g (10 mmol) of **2** was added over a 10-min period 10 ml of 1.0 *N* NaOH. After a total of 17 min the cloudy solution was filtered and 10 ml of 1.0 *N* HCl was added. The pH was adjusted to 4 with NaOH and the mixture was stored for 0.5 hr at 0°. The crystals were collected, washed with 1–2 ml of $H_2O$, and dried at 100°, 1.64 g (72%), mp 235–240° dec. Recrystallization from $H_2O$ gave a hydrate which was dehydrated *in vacuo* at 80°: p$K_1'$ (50% EtOH) = 2.00 (proton gained), p$K_2$ = 5.86 (proton lost); ir (mineral oil) 2700, 1900 ($NH_3^+$), 1580 $cm^{-1}$ (s, $COO^-$); nmr (DMSO-$d_6$) AB quartet $\delta$ 4.50, 4.75 ($J$ = 8 Hz, 2 H, $C_{4,5}$ protons), 7.4 (s, 5 H, phenyl); nmr (TFA-*d*) 5.65 (s, 2 H, $C_{4,5}$ protons), 7.5 (m, 5 H, phenyl); uv max (pH 9.0) $\lambda_{max}^{0.05\ M\ Tris}$ 2700 nm ($\epsilon$ 259), 2635 (351), 2570 (306); for **1**, $\lambda_{max}^{0.05\ M\ Tris}$ 2700 nm ($\epsilon$ 246), 2630 (346), 2570 (302).

*Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38; S, 14.17. Found: C, 47.75; H, 4.36; N, 12.36; S, 14.39.

**Epimerization of 3.**—To 203 mg (0.90 mmol) of **3** was added 2 ml of 0.50 *N* NaOH. After 30 min, 1.0 ml of 1.0 *N* HCl was added; the solution was stored at 4°, and the crystals were collected and dried at 100°, 129 mg (63%). The filtrate was evaporated to dryness *in vacuo*, 71 mg. Each fraction gave an ir spectrum virtually identical with that of **5** prepared from **7**.

***erythro*-*N*-Acetyl-3-sulfamyl Phenylalanine Methyl Ester (9).**—Anhydrous HCl was added to 2.0 g (7.5 mmol) of *trans* 4-acetamido-5-phenyl-3-isothiazolidinone 1,1-dioxide[1] (**6**, previously identified[1] as cis) in 50 ml of methanol over a 15-min period. The hot solution was stored at 25° for 20 min and then evaporated *in vacuo*. To the residue was added 25 ml of 0.6 *M* $NaHCO_3$ (pH 7–8). The precipitate was collected, washed with water, and dried *in vacuo*, 1.1 g (49%), mp 147–150° dec. Recrystallization from 3 ml of methanol raised the melting point to 150–151° dec; ir (mineral oil) 3550, 3450, 3300, 3200 (–NH), 1730 (s, ester C=O), 1675 $cm^{-1}$ (s, amide C=O).

*Anal.* Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33; S, 10.68. Found: C, 47.87; H, 5.35; N, 9.55; S, 10.92.

***erythro*-3-Sulfamyl Phenylalanine Methyl Ester (7).**—To 50 ml of methanol saturated with anhydrous HCl was added 3.0 g (11.2 mmol) of **6**. The solution was refluxed for 2 hr and evaporated *in vacuo* to a gum, to which was added 30 ml of 0.6 *M* $NaHCO_3$ (pH 8). The cloudy solution was evaporated to 15 ml, decolorized with Darco, and stored overnight at 4°. The precipitate was collected, washed with water, and dried at 25°, 1.25 g. The ir spectrum showed the product to be mainly **7** but with some contamination by **9**. Several recrystallizations from methanol afforded pure **7**: mp 154–155 dec; p*K* (proton gained) = 4.81; ir (mineral oil) 3400, 3300, 3250 (NH), 1710 $cm^{-1}$ (s, ester C=O).

*Anal.* Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.36; H, 5.41; N, 10.72; S, 12.53.

***trans*-4-Amino-5-phenyl-3-isothiazolidinone 1,1-Dioxide (5).**—To 582 mg (2.25 mmol) of **3** was added 2.20 ml of 1.0 *N* NaOH. The solution was heated to 50° for 10 min, 2.20 ml 1.0 *N* HCl was added, and the mixture was chilled. The crystals were collected and washed with a little $H_2O$: 360 mg (71%), mp 246–248° dec. Recrystallization from $H_2O$ raised the melting point to 258–260° dec. Neither ir nor nmr spectra showed any evidence of the cis epimer [p$K_1$ (50% EtOH) = 2.29, p$K_2$ = 6.15]: ir (mineral oil) 2500, 1950, 1630 (s, $NH_3^+$), 1590 $cm^{-1}$ (s, $COO^-$); nmr (DMSO-$d_6$) 4.56 (s, 2 H, $C_{4,5}$ protons), 7.45 (s, 5 H, phenyl); nmr (TFA-*d*) AB quartet $\delta$ 5.60 and 5.40 ($J$ = 11 Hz, 2 H, $C_{4,5}$ protons), 7.6 (s, 5 H, phenyl); uv max (pH 9.0) $\lambda_{max}^{0.05\ M\ Tris}$ 269 nm ($\epsilon$ 158), 263 (237), 259 (271); for **2**, $\lambda_{max}^{0.05\ M\ Tris}$ 270 nm ($\epsilon$ 174), 263 (254), 259 (286).

*Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38; S, 14.17. Found: C, 47.86; H, 4.32; N, 12.37; S, 14.05.

**Synthesis of 6 from 9.**—To 225 mg (0.75 mmol) of **9** was added 0.75 ml of 1 *N* NaOH. The solution was filtered from some cloudiness and after 15 min strongly acidified with HCl and chilled. The crystals were collected and dried, 111 mg (53%) mp 223–225°. The ir spectrum showed no evidence of the cis epimer.

**Epimerization of 1.**—To 57 mg (0.21 mmol) of **1** was added 1.0 ml of 1.0 *N* NaOH. After 6 min at 25° 0.5 ml of 12 *N* HCl was added and the solution was chilled and filtered. The crystals were washed with a little $H_2O$ and dried *in vacuo* at 80°, 44 mg (77%); the ir spectrum was identical with that of **6**.[1]

**Registry No.**—**1**, 36529-48-3; **2**, 36529-49-4; **3**, 36529-50-7; **5**, 36529-51-8; **6**, 36529-52-9; **7**, 36529-53-0; **9**, 36529-54-1.

**Acknowledgment.**—We are grateful to the National Science Foundation for Grants GB 4043 and GB 7267, which made this work possible.

(8) D. J. Cram and T. A. Whitney, *J. Amer. Chem. Soc.*, **89**, 4651 (1967).

(9) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 605–607.

# $\Delta^2$-2,3-Dipropylcyclopropenyldiazomethanes. Generation from Nitrosourethane and Hydrazone Precursors[1a]

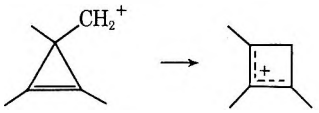
ANDREW E. FEIRING[1b] AND JOSEPH CIABATTONI*

*Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island 02912*

*Received May 23, 1972*

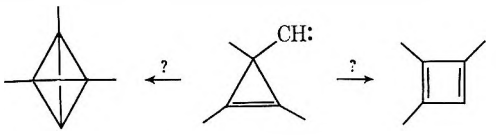
The decomposition of methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl)-*N*-nitrosourethane (**2**) with several bases has been studied. With potassium *tert*-butoxide the corresponding potassium diazotate salt is formed *via* carbonyl carbon attack. Hydrolysis leads only to carbonium ion products. With lithium ethoxide and sodium methoxide, attack at the nitroso N leads to 3,4-dipropylpyridazine (**8**) and methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl) carbonate (**6**) as major products *via* the corresponding diazocarbonate **10**. Cyclopropenyldiazomethane **11** is implicated as an intermediate in the formation of **8**. Oxidation of methyl ($\Delta^2$-2,3-dipropylcyclopropenyl) ketohydrazone (**3**) with lead tetraacetate affords methyl ($\Delta^2$-2,3-dipropylcyclopropenyl)carbinyl acetate (**15**). With mercuric oxide, **3** gives 3,4-dipropyl-6-methylpyridazine (**17**). Both reactions appear to involve the corresponding cyclopropenyldiazoalkane **16**.

While a great deal of attention has been focused in recent years on the cyclopropylcarbinyl system, relatively little work has been reported on the chemistry of the cyclopropene ring when joined to an unsaturated center.[2] The solvolysis of diphenyl- and dipropylcyclopropenylcarbinyl alcohol derivatives[3,4] is reported to afford products derived from the cyclobutenyl cation, which results from ring expansion. Although an analysis[3] of kinetic data suggested that the transition state for solvolysis has considerable cyclopropenylcarbinyl character, no report of the successful trapping of this species has appeared.[5]



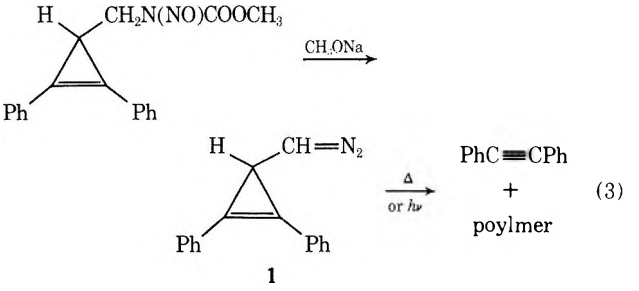

(1)

The reactivity of a carbenoid center adjacent to a cyclopropene ring is also of interest because of the formal relationship (eq 2) of a cyclopropenylcarbene




(2)

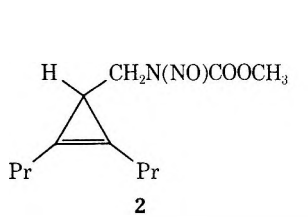
to cyclobutadiene[6] and tetrahedrane.[7] Closs and Rao[8] have reported that dimers of cyclobutadiene are formed in high yields by treatment of 1,2,3-trimethyl-3-(dichloromethyl)cyclopropene with *n*-butyllithium. White and coworkers[7a] attempted to generate diphenyltetrahedrane from diphenylcyclopropenyldiazomethane (**1**). The diazoalkane **1** was prepared by treating the corresponding nitrosourethane (eq 3) with "solid

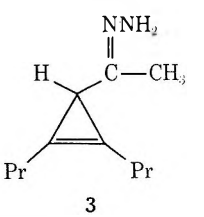



(3)

sodium methoxide containing some methanol of solvation." The thermal and photochemical decomposition of **1** leads mainly to diphenylacetylene and polymer. Masamune and Kato[7b] photolyzed the sodium salt of 1,2-diphenylcyclopropene-3-carboxaldehyde tosylhydrazone and obtained acetylene, diphenylacetylene, and a trace amount of a cyclobutenophenanthrene.

We have been interested for some time in the reactivity of a carbene adjacent to an alkyl-substituted cyclopropene. Of the variety of methods available for the generation of carbenes, the thermal decomposition of an $\alpha$-diazocyclopropene seemed most appropriate in this case. Diazoalkanes are generally prepared[9] by the base-induced decomposition of *N*-nitrosourethanes or by hydrazone oxidation. We have prepared methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl)-*N*-nitrosourethane (**2**) and methyl ($\Delta^2$-2,3-dipropylcyclopropenyl) ketohydrazone (**3**). In this paper we




report on the novel results obtained from studies on the decomposition of **2** using different alkoxide systems and on the oxidation of **3** with lead tetraacetate and mercuric oxide.

(1) (a) Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstract ORGN 154. (b) National Science Foundation Graduate Trainee, 1970–1971.

(2) R. Breslow in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 233–295.

(3) R. Breslow and M. Battiste, *J. Amer. Chem. Soc.*, **82**, 3626 (1960); R. Breslow, J. Lockhart, and A. Small, *ibid.*, **84**, 2793 (1962).

(4) (a) P. Wolf, Ph.D. Thesis, Columbia University, 1964; (b) R. Breslow, H. Bozimo, and P. Wolf, *Tetrahedron Lett.*, 2395 (1970).

(5) A somewhat specialized case of the reverse rearrangement, *i.e.*, cyclobutenyl to cyclopropenylcarbinyl, has recently been discovered in this laboratory: J. Ciabattoni and A. E. Feiring, *J. Amer. Chem. Soc.*, **94**, 5113 (1972).

(6) M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967.

(7) (a) E. H. White, G. E. Maier, R. Graeve, U. Zernibl, and E. W. Friend, *J. Amer. Chem. Soc.*, **88**, 611 (1966). (b) S. Masamune and M. Kato, *ibid.*, **87**, 4190 (1965); **88**, 610 (1966). (c) Additional attempts to generate tetrahedrane include H. W. Chang, A. Lautzenheiser, and A. P. Wolf, *Tetrahedron Lett.*, 6295 (1966); R. F. Peterson, R. T. K. Baker, and R. L. Wolfgang, *ibid.*, 4749 (1969); P. B. Shelvin and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 406 (1970); H. Ona, H. Yamaguchi, and S. Masamune, *ibid.*, **92**, 7495 (1970); H. J. Hageman and U. E. Wiersum, *Chem. Commun.*, 497 (1971); M. S. Newman and M. W. Logue, *J. Org. Chem.*, **36**, 1398 (1971), and references cited therein.

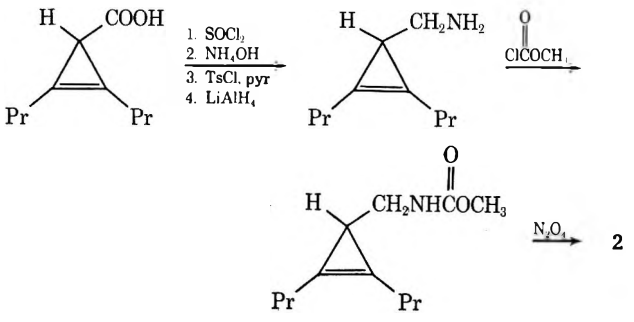
(8) G. L. Closs and V. N. M. Rao, *J. Amer. Chem. Soc.*, **88**, 4116 (1966).

(9) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961, Chapter 1.

## Results and Discussion

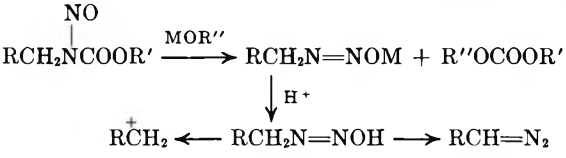
**Decomposition of 2.**—Methyl *N*-(Δ²-2,3-dipropylcyclopropenylcarbinyl)urethane was prepared from Δ²-2,3-dipropylcyclopropenecarboxylic acid[10] *via* the acid chloride, the amide, the nitrile, the amine, and reaction of the amine with methyl chloroformate (Scheme I). The *N*-nitrosourethane **2** was prepared

SCHEME I




by nitrosation of the urethane with dinitrogen tetroxide.[11] The nitrosourethane was purified by chromatography over silica gel and showed no detectable impurities by nmr or tlc.

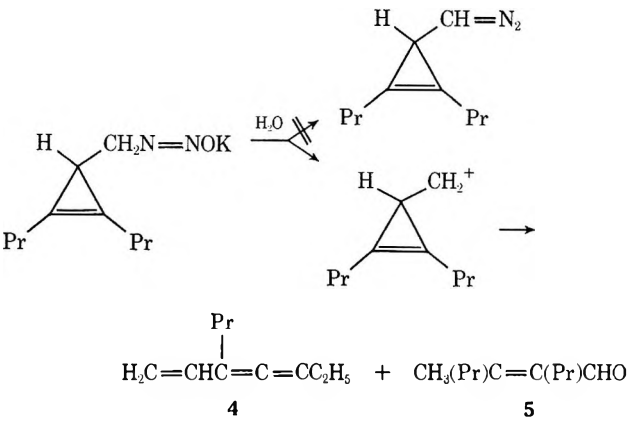
The reaction of alkoxide bases on nitrosourethanes is known to proceed *via* initial attack of base on either the carbonyl carbon or the nitroso N, depending on the type of substrate, base, and solvent used.[12] Attack of base at the carbonyl carbon affords a diazotate salt which is isolatable in the absence of a proton source. Protonation[13] of the diazotate salt affords a diazotic acid which partitions between diazoalkane and carbonium ion formation depending upon the structure of the alkyl group and the nature of the reaction medium. In 1966, Moss[13] reported that treatment of nitrosourethanes with potassium *tert*-butoxide in ether




affords, *via* carbonyl attack, the corresponding potassium diazotate salts. For the particular case of the dipropylcyclopropenylcarbinyl system (Scheme II), hydrolysis of the diazotate salt afforded none of the expected diazoalkane but exclusively products **4** and **5** derived from a cyclopropenylcarbinyl cation.[4a] In our hands, addition of **2** to a slurry of potassium *tert*-butoxide in ether resulted in rapid disappearance of the yellow nitrosourethane color but no gas evolution. Subsequent hydrolysis after 20 min resulted in vigorous $N_2$ evolution. Glpc examination of the colorless ethereal solution was consistent with that reported[13] (Scheme II). No trace of diazoalkane could be detected.

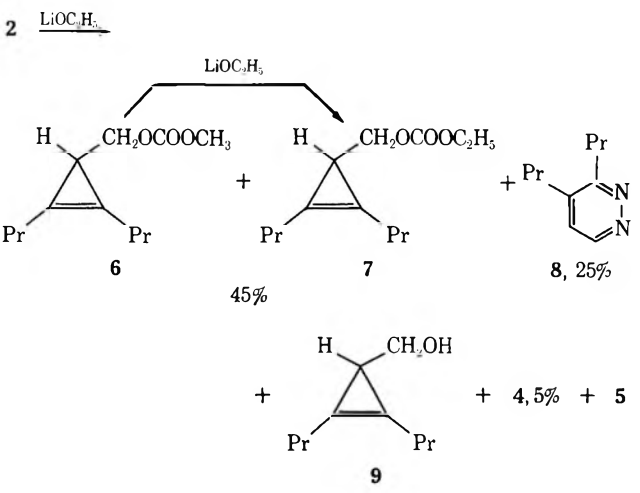
In contrast, addition of **2** to an ethereal slurry of anhydrous lithium ethoxide resulted in the gradual (*ca.* 0.5 hr) evolution of 75% of the theoretical yield of $N_2$. Conventional isolation procedures afforded

SCHEME II




methyl (Δ²-2,3-dipropylcyclopropenylcarbinyl) carbonate (**6**), ethyl (Δ²-2,3-dipropylcyclopropenylcarbinyl)-carbonate (**7**) (combined yields of **6** + **7**, 45%), 3,4-dipropylpyridazine (**8**, 25%), 3-propyl-1,3,4-heptatriene (**4**, 5%), and trace amounts of Δ²-2,3-dipropylcyclopropenylcarbinyl alcohol (**9**) and *cis*- and *trans*-2-propyl-3-methyl-2-hexenal (**5**) (Scheme III). Appropriate control experiments demonstrated that ethyl carbonate **7** and alcohol **9** were secondary products arising from attack of ethoxide ion on the initially formed methyl carbonate **6**. The relative amounts of **6** and **7** varied as a function of reaction time; a longer reaction time increased the yield of **7** at the expense of **6**.

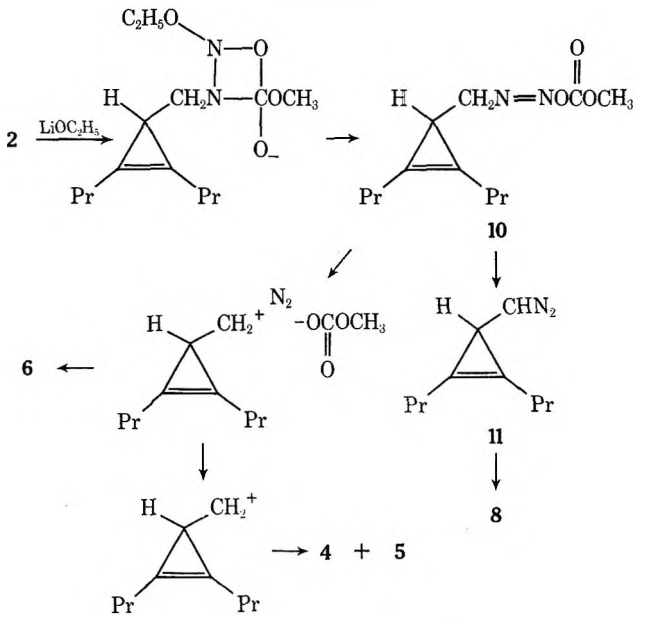
SCHEME III




The results of the lithium ethoxide decomposition of **2** are most readily explained by assuming initial attack of base on the nitroso N[12] to generate a cyclic intermediate (Scheme IV) followed by ring opening to generate the diazocarbonate **10**. Intermediate **10** is similar to that proposed in the thermal decomposition of nitrosoamide derivatives.[14] The nature of the products indicates two modes of decomposition of **10**. Loss of nitrogen generates a cyclopropenylcarbinyl cation–carbonate anion ion pair which, in the nonpolar solvent, largely collapses to **6** before rearrangement can occur. The small amounts of rearranged carbonium ion products (*i.e.*, **4** and **5**) result from the

(10) R. Breslow, H. Hover, and H. W. Chang, *J. Amer. Chem. Soc.*, **84**, 3168 (1962).
(11) E. H. White, *ibid.*, **77**, 6008 (1955).
(12) W. M. Jones and D. L. Muck, *ibid.*, **88**, 3798 (1966).
(13) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).
(14) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 440–458.

SCHEME IV

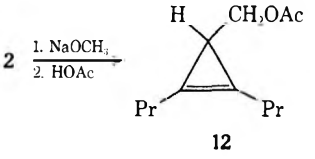


small proportion of cyclopropenylcarbinyl cation which escapes from the solvent cage before collapse to **6**. A second mode for decomposition of **10** is suggested by the formation of pyridazine **8**. Under the basic reaction conditions, loss of an $\alpha$ proton from **10** followed by or simultaneous with loss of carbonate anion generates diazoalkane **11**. Thermal rearrangement of **11** affords the observed regiospecific 3,4-dipropylpyridazine (**8**). Apparently the rate of rearrangement of **11** is competitive with its rate of formation, as its presence under the above conditions (*vide infra*) could not be directly detected. Quenching of a reaction mixture with acetic acid before completion afforded only a mixture of the above products plus unchanged starting material.

While we have not been able to obtain direct evidence for this mechanism, it appears attractive for several reasons. First, it accounts for $N_2$ loss and product formation prior to hydrolysis. Second, the observation of a high percentage of carbonate product with the unrearranged cyclopropenylcarbinyl system appears to require some intermediate (*i.e.*, **10**) which can efficiently produce a cyclopropenylcarbinyl cation–carbonate anion ion pair under the reaction conditions. If intermolecular attack by carbonate anion on some other intermediate were the source of **6**, the lack of observed products arising from attack of the more nucleophilic ethoxide ion, present in excess, is difficult to explain. Finally the rearrangement of **11** to **8** has precedent[2] in other rearrangements of cyclopropene derivatives to form six-membered rings. Although the tendency for lithium alkoxide bases to promote attack on the nitroso N has been previously observed,[12] we are unaware of another example in which the change in base effects the radical change in product composition observed in this case.

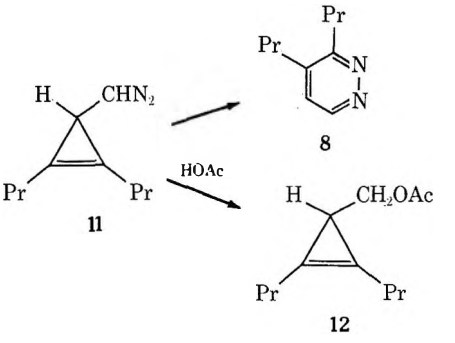
More definitive evidence for the intermediacy of diazoalkane **11** was obtained by decomposition of **2** with sodium methoxide. Addition of **2** to an ethereal slurry of sodium methoxide containing some methanol[7a] resulted in a rapid (*ca.* 5 min) evolution of 52% of the theoretical yield of $N_2$ and the simultaneous formation of a pink color in the ether solution. An infrared spectrum of the mixture at this point showed a strong band at 2050 $cm^{-1}$ consistent with the presence of diazoalkane. After several hours the color faded with little additional gas evolution. The products, in addition to considerable quantities of nonvolatile residue, were **6** (15%), **8** (15%), **4**(15%), and a large number of trace products (by glpc), two of which were identified as alcohol **9** and unsaturated aldehyde **5**. Examination of the crude reaction mixture by glpc indicated the absence of 4-octyne and methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl) ether in the mixture (the latter was independently synthesized for comparison of glpc retention times). Despite the fact that nmr of the crude mixture showed complete destruction of the nitrosourethane, only 12% dimethyl carbonate was detected by glpc.

Quenching of a 5-min-old slurry of **2** and sodium methoxide in ether with excess glacial acetic acid produced a second vigorous evolution of $N_2$ and immediate disappearance of the pink color. Nmr of the crude mixture (which in this case contained little nonvolatile material) showed complete destruction of the nitrosourethane **2**. Glpc of the reaction mixture was compatible with that obtained above, except that in this case no pyridazine **8** was present. Instead a new product, comprising 38% of the mixture by glpc, was present, which was collected by preparative glpc and identified as $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl acetate (**12**).



**12**

The isolation of only 12% dimethyl carbonate from the sodium methoxide decomposition of **2** suggests that this reaction also proceeds largely from attack of base on the nitroso N (Scheme IV). In this case, however, formation of the diazoalkane **11** appears to be much faster than in the lithium ethoxide case. This results in a buildup of **11** in solution, as evidenced by the solution color and infrared spectrum. The isolation of acetate **12** confirms the structure of **11**,



as diazoalkanes are known to react rapidly with carboxylic acids to give unrearranged product esters.[15] Furthermore, the fact that the acetic acid quench eliminated formation of the pyridazine **8** with little effect on the other reaction products suggests that pyridazine alone arises from the diazoalkane intermediate.

It is interesting to note that little nonvolatile ma-

(15) D. Y. Curtin and S. M. Gerber, *J. Amer. Chem. Soc.*, **74**, 4052 (1952).

terial was obtained from the reaction mixture quenched by acetic acid and that the residue from the mixtures which were allowed to proceed without quenching showed a strong band at 1640 $cm^{-1}$ in the infrared. These facts suggest that azine formation may be partially responsible for the low overall product yields in the sodium methoxide case. Quenching the mixture with acetic acid is seen to eliminate azine formation as well as pyridazine formation, accounting for the somewhat higher yield of acetate **12** (38% by glpc) as compared to the yield of pyridazine in unquenched reactions (20% by glpc, see Experimental Section). The somewhat cleaner results obtained from the lithium ethoxide reaction may, therefore, be due in part to slower initial attack of base on the nitrosourethane. The rate of formation of diazoalkane is roughly the same as its rate of unimolecular rearrangement to pyridazine; its concentration in solution remains low, thereby largely eliminating bimolecular reaction to form azine. The reason for the difference in rate of attack by lithium ethoxide and sodium methoxide is, however, not known.

The possibility that some of the results reported here might be due to a thermal decomposition of nitrosourethane **2** was ruled out by the finding that **2** was completely stable to the reaction conditions in the absence of base for over 24 hr (no detectable impurities by nmr). The compound could be recovered in pure form in 73% yield by column chromatography after 24-hr reflux in cyclohexane.

**Oxidation of 3.**—Oxidation[9] of the hydrazone of $\Delta^2$-2,3-dipropylcyclopropenecarboxaldehyde (**13**) was expected to provide an independent synthesis of the diazoalkane **11** implicated in the alkoxide decomposition of **2**. The aldehyde **13** was prepared as shown in Scheme V. The reduction of $\Delta^2$-2,3-dipropylcyclopropenecarboxylic acid[10] with $LiAlH_4$ is reported[4a] to lead to a mixture of the cyclopropenylcarbinyl alcohol **9** and a saturated alcohol arising from homoconjugate reduction of the double bond. We have found that carrying out the reduction in ether at $-40°$ eliminates overreduction, providing in high yield the desired unsaturated alcohol **9**. Careful oxidation of **9** with dipyridine–chromium trioxide complex in methylene chloride (the Collins reagent[16]) afforded the aldehyde **13**. In our hands, however, the aldehyde was a rather unstable oil which was difficult to purify and did not provide satisfactory derivatives.

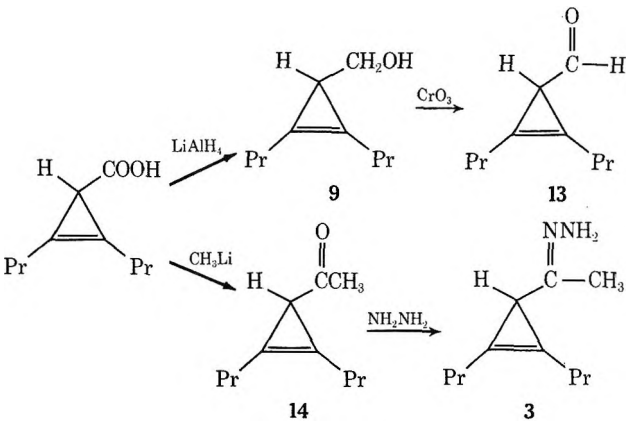
We turned out attention, therefore, to the corresponding methyl ketone **14**, which was prepared according to published procedures[17] from $\Delta^2$-2,3-dipropylcyclopropenecarboxylic acid and methyllithium. Treatment of **14** with excess hydrazine in methanol afforded, in excellent yield, the corresponding hydrazone **3** as a colorless oil which decomposed rapidly neat but was stable for prolonged periods in solution. It could be recovered unchanged after refluxing for 8 hr in ethanol.[18] The samples used for oxidation were freshly prepared and contained no detectable impurities by nmr or ir spectroscopy.

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

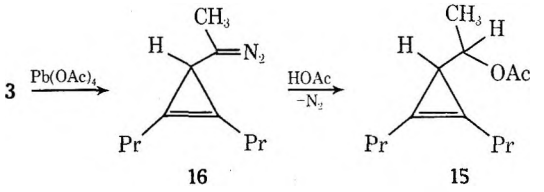
(17) M. Vidal, E. Chollet, and P. Arnaud, *ibid.*, 1073 (1967).

(18) Phenyl ($\Delta^2$-2,3-dipropylcyclopropenyl) ketohydrazone is reported to rearrange under the conditions of its synthesis (refluxing ethanol) to a dihydropyridazine: R. Breslow, R. Boikess, and M. Battiste, *ibid.*, **No. 26**, **42** (1960); N. Obata and I. Moritani, *Bull. Chem. Soc. Jap.*, **39**, 2250 (1966).

SCHEME V

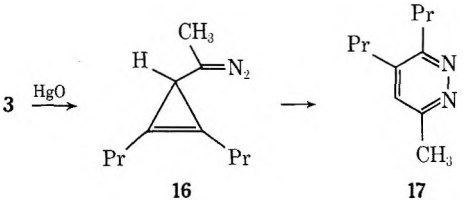



Addition of a methylene chloride solution of **3** to a slight excess of lead tetraacetate[19] in methylene chloride resulted in immediate nitrogen evolution and formation of a white precipitate of lead diacetate. Conventional isolation procedures involving silica gel chromatography afforded a 51% yield of methyl ($\Delta^2$-2,3-dipropylcyclopropenyl)carbinyl acetate (**15**). This reaction is believed to involve[19] oxidation of the hydrazone to the corresponding diazoalkane **16** fol-




lowed by reaction of the diazoalkane with the *in situ* generated acetic acid. As in the case of the sodium methoxide decomposition of **2** followed by quenching with acetic acid, reaction of the diazoalkane with acid is faster than rearrangement to a pyridazine.

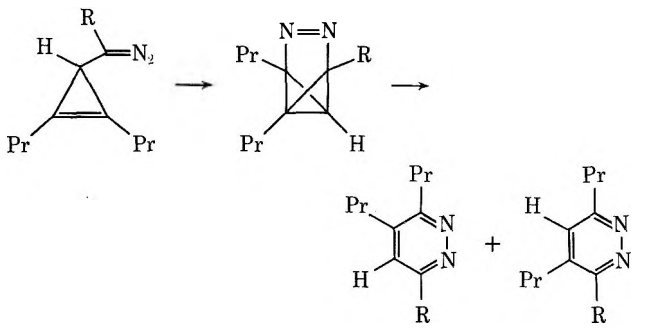
Pyridazine product, however, was obtained from the mercuric oxide oxidation of **3**. Stirring a suspension of red mercuric oxide and hydrazone **3** at high speed for 24 hr in pentane resulted in little gas evolution. Work-up afforded in 58% isolated yield (67% by nmr of the crude reaction mixture) an oil the structure of which was assigned as 3,4-dipropyl-6-methylpyridazine (**17**).




These results, when combined with those from the alkoxide-induced decomposition of **2**, leave little doubt that dipropylcyclopropenyldiazomethanes rearrange with reasonable efficiency to the corresponding pyridazines. The mechanism of this rearrangement appears to involve a formal 1,4-sigmatropic shift of a cyclopropene $\sigma$ bond. An alternate possibility (Scheme VI) that rearrangement involves an intramolecular 1,3-dipolar cycloaddition of the diazoalkane group to

(19) D. H. R. Barton, J. F. McGhie, and P. L. Batton, *J. Chem. Soc. C*, 1033 (1970).

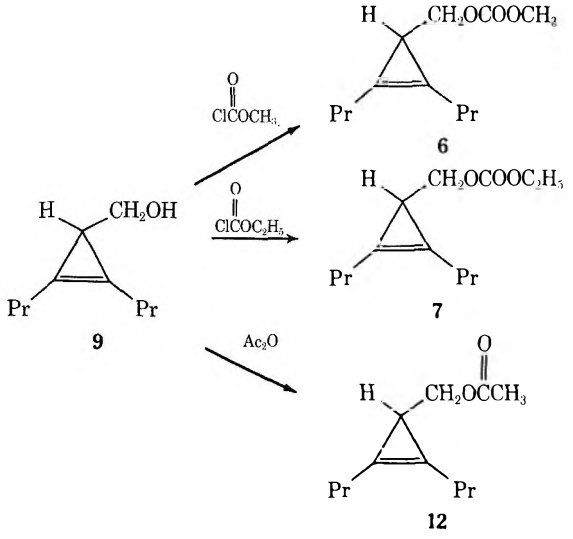
SCHEME VI



the cyclopropene double bond[20] followed by a bicyclobutane–butadiene type of rearrangement[21] is less likely, since it should lead to the production of two isomeric pyridazines, contrary to what was observed.

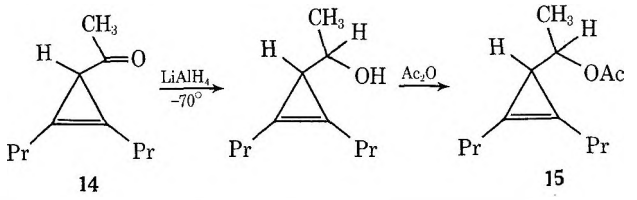
It is interesting to note that, for diphenylcyclopropenyldiazomethane,[7a] nitrogen loss followed by or simultaneous with fragmentation to acetylene and diphenylacetylene is the major mode of decomposition, whereas in the dipropyl case rearrangement to pyridazine predominates (no 4-octyne was detected in any experiment).

**Product Identification.**—In addition to their nmr and ir spectra (see Experimental Section), the identities of reaction products which are derivatives of $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl alcohol (**9**) were confirmed by independent synthesis. Treatment of **9** with methyl or ethyl chloroformate in pyridine afforded samples of **6** and **7**, respectively, identical with the products from the lithium ethoxide induced decomposition of **2**. Acylation of **9** with acetic anhydride afforded in acetate identical with **12**.



Lithium aluminum hydride reduction of methyl ($\Delta^2$-2,3-dipropylcyclopropenyl) ketone at −70°, followed by acylation with acetic anhydride in pyridine, afforded an acetate **15** identical with the product from the lead tetraacetate oxidation of hydrazone **3**.

The pyridazine structure **8** was assigned on the basis of the following data. Elemental analysis and mass spectrum (*m/e* 164) were consistent with the formula $C_{10}H_{16}N_2$. A prominent ion at *m/e* 136 ($M^+ - N_2$)



was also observed in the mass spectrum.[22] The ir showed sharp absorptions at 1580 and 1560 $cm^{-1}$, and the uv showed maxima at 254, 258, and 335 m$\mu$, characteristic of the pyridazine structure.[23] The nmr spectrum, in addition to two nonequivalent propyl groups, showed clean one-proton doublets at 7.27 and 8.92 ppm with a coupling constant of 5.2 Hz. The chemical shifts and coupling constants of the aromatic protons are consistent only with the assigned pyridazine substitution pattern; the observed coupling constants for pyridazine protons are $J_{3,4} = 5.05$ and $J_{3,5} = 2.0$ Hz.[23]

In a similar fashion, the elemental analysis and mass spectrum (*m/e* 178) of **17** established its formula as $C_{11}H_{18}N_2$. Its ir and uv spectra closely resembled those obtained for pyridazine **8**. The nmr showed, in addition to the nonequivalent propyl groups, sharp singlets at 2.62 ($CH_3$) and 7.10 ppm (aromatic H).

Structural assignments for **4** and **5** are based on their glpc and spectroscopic (ir and nmr) identity with the major products from the potassium *tert*-butoxide decomposition of **2**.[13]

## Experimental Section

Melting points were obtained on a Kofler micro heating stage; all melting and boiling points are uncorrected. Infrared and ultraviolet spectra were recorded with a Perkin-Elmer 337 spectrophotometer and a Cary Model 14 recording spectrophotometer, respectively. Infrared spectra were recorded as films unless otherwise indicated; only bands important for structure proof are reported. All nmr spectra were run on a Varian A-60A instrument in the indicated solvents. Chemical shifts are reported in parts per million from tetramethylsilane and the number in parentheses indicates the number of protons responsible for the signal. The letter denotes the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet. Mass spectra were obtained with an Hitachi RMU-6D instrument. Gas–liquid partition chromatographic (glpc) analyses were obtained with an Aerograph A-90P instrument using a 10 ft × 0.25 in. column of 15% SE-30 on Chromosorb W. Relative peak areas were measured by disk integration and are not corrected for detector response.

Gas evolution was measured by water displacement; reported volumes are corrected for the vapor pressure of water and to standard conditions of temperature and pressure. All reactions were run in an atmosphere of prepurified nitrogen or argon.

The purity of all new compounds was checked by glpc or tlc, and, where stability permitted, by elemental analysis (Galbraith Laboratories, Knoxville, Tenn.).

**Materials.**—Ethyl ether, benzene, and hydrocarbon solvents were freshly distilled from $LiAlH_4$. Pyridine was distilled from BaO. The following reagents were obtained from the indicated source and were used as received: anhydrous sodium methoxide (Matheson Coleman and Bell), anhydrous potassium *tert*-butoxide (MSA Research Corp.), methyllithium (Alfa), lithium ribbon (City Chemical Corp.), dinitrogen tetroxide ("nitrogen dioxide," Matheson), methyl and ethyl chloroformate (Aldrich), 4-octyne (Farchan), mercuric oxide (Baker). Lead tetraacetate (G. Fredrich Smith Co.) was recrystallized from glacial acetic acid and dried *in vacuo* immediately before use. Tosyl chloride

(20) H. M. Cohen, *J. Heterocycl. Chem.*, **4**, 130 (1967).
(21) G. L. Closs and P. E. Pfeffer, *J. Amer. Chem. Soc.*, **90**, 2452 (1968).
(22) S. J. Weininger and E. R. Thornton, *ibid.*, **89**, 2050 (1967); M. H. Benn, T. S. Saensen, and A. M. Hagg, *Chem. Commun.*, 574 (1967).
(23) M. Tisler and B. Stanovnik in "Advances in Heterocyclic Chemistry," Vol. 9, A. R. Katritsky and A. J. Baulton, Ed., Academic Press, New York, N. Y., 1968.

was purified according to Fieser.[24] Lithium ethoxide was prepared according to a published procedure.[25] The product was dried for 6 hr at 100° (2 mm) and used immediately. Column chromatography was performed using Baker 60–200 mesh silica gel; thin layer chromatography (tlc) was performed on precoated silica gel plates purchased from E. Merck & Co.

**$\Delta^2$-2,3-Dipropylcyclopropenecarboxamide.**—Freshly distilled thionyl chloride (25 ml) was added dropwise over 0.5 hr to a stirred solution of 25.2 g (0.15 mol) of $\Delta^2$-2,3-dipropylcyclopropenecarboxylic acid[10] in 25 ml of benzene. The dark mixture was then refluxed under nitrogen for 3 hr and cooled and the benzene and excess thionyl chloride were removed *in vacuo*. The dark brown oil was distilled to give the colorless acid chloride: bp 72° (0.5 mm) [lit.[26] bp 59–61° (0.2 mm)]; ir 1900 (w), 1780 $cm^{-1}$ (s).

The acid chloride was dissolved in 100 ml of ether and added dropwise to a stirred mixture of 300 ml of concentrated $NH_4OH$ and 600 ml of ether. The layers were separated and the aqueous solution was extracted once with 50 ml of ether. The combined ether solutions were washed twice with water and twice with saturated aqueous NaCl solution. Evaporation of the ether *in vacuo* left a white solid which was recrystallized from cyclohexane to give 21 g (85%) of white needles: mp 107–109° (lit.[26] mp 106–106.5°); ir (KBr) 3350 (s), 3275 (s), 1890 (w), 1630 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.55 (4 H, m), 1.95 (1 H, s), 2.43 (4 H, t), 6.0 (2 H, bs).

**1-Cyano-2,3-dipropylcycloprop-2-ene.**—Freshly purified tosyl chloride[24] (22.9 g, 0.12 mol) was added portionwise over 0.5 hr to a stirred solution of 14 g (0.084 mol) of $\Delta^2$-2,3-dipropylcyclopropenecarboxamide in 125 ml of dry pyridine. The solution temperature was maintained between 5 and 10° by means of an ice bath. A thick precipitate which formed during the addition required that an additional 50 ml of pyridine be added to maintain stirring. The mixture was stirred at 5° for 45 min after the addition was complete. The mixture was then poured into 300 ml of water and the aqueous solution was extracted with three 100-ml portions of ether. The combined ether extracts were washed with 5% aqueous HCl, water, and saturated aqueous NaCl and dried ($MgSO_4$). Evaporation of the ether *in vacuo* left a faintly brown oil which was distilled to give 11.6 g (93%) of colorless nitrile: bp 72° (0.9 mm); ir 2220 (m), 1880 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.55 (4 H, m), 1.68 (1 H, s), 2.43 (4 H, t).

**$\Delta^2$-2,3-Dipropylcyclopropenylcarbinylamine.**—A solution of 14.9 g (0.1 mol) of 1-cyano-2,3-dipropylcycloprop-2-ene in 30 ml of dry ethyl ether was added dropwise over 0.5 hr to a rapidly stirred suspension of 4.5 g (0.12 mol) of $LiAlH_4$ in 90 ml of ether at 0°. After the addition was complete, the mixture was stirred at 0° for 5 hr. Excess hydride was decomposed by the dropwise addition of 10% NaOH solution. The white granular precipitate which formed was filtered off and washed with fresh ether. The combined ether solutions were washed with saturated aqueous NaCl and dried ($MgSO_4$). Evaporation of the ether *in vacuo* left a faintly brown oil which was distilled to give 12.1 g (79%) of amine: bp 82° (20 mm); ir 3360 (m), 3280 (m), 1860 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 0.97 (8 H, t + s), 1.55 (5 H, m), 2.43 (4 H, t), 2.63 (2 H, d). Treatment of the nmr sample with $D_2O$ caused a two proton decrease in the integral at $\delta$ 0.97.

The amine was converted to its hydrochloride with HCl in ether; after three recrystallizations from ether–pentane it melted at 134–135°.

*Anal.* Calcd for $C_{10}H_{20}NCl$: C, 63.29; H, 10.62; N, 7.32. Found: C, 63.33; H, 10.47; N, 7.18.

**Methyl *N*-($\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl)urethane.**—Excess methyl chloroformate (4 ml) was added dropwise over 10 min to a stirred solution of 3.33 g (22 mmol) of $\Delta^2$-2,3-dipropylcyclopropenylcarbinylamine, 30 ml of benzene, and 5 ml of dry pyridine cooled in an ice bath. When the addition was complete, the ice bath was removed and the mixture was stirred for an additional 0.5 hr. The mixture was poured into ice water (100 ml) and the layers were separated. The aqueous solution was washed once with benzene. The combined organic layers were washed with cold 5% aqueous HCl, 10% aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried ($MgSO_4$). Evaporation of the benzene *in vacuo* left a brown oil which was distilled to yield 3.7 g (82%) of colorless urethane: bp 81–83° (0.4 mm); ir 3340 (s), 1850 (w), 1700 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.55 (5 H, m), 2.43 (4 H, t), 3.10 (2 H, t), 3.59 (3 H, s), 5.87 (1 H, bs).

*Anal.* Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 67.86; H, 9.72.

**Methyl *N*-($\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl)-*N*-nitrosourethane (2).**—Dinitrogen tetroxide (2 ml, 3 g) was condensed in a calibrated trap at −40°. The trap was then warmed to room temperature and the $N_2O_4$ was distilled into 100 ml of dry ether at −20° to give a *ca.* 0.32 *M* solution.

A 100-ml round-bottom flask, equipped with magnetic stirring, thermometer, and gas inlet extending to the bottom of the flask, was charged with 1.37 g (6 mmol) of methyl *N*-($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl)urethane, 0.88 g (10 mmol) of anhydrous NaOAc, and 30 ml of dry ethyl ether. The mixture was cooled to −70° with a Dry Ice–acetone bath and argon was slowly bubbled into the solution. To this vigorously stirred mixture was added 30 ml (*ca.* 10 mmol) of the precooled $N_2O_4$ in ether solution by means of a syringe. The green solution which resulted was stirred under argon at −70° for 1.25 hr. The solution was then poured with stirring into 50 ml of 5% aqueous $NH_4OH$ and the layers were separated. The organic layer was washed with 10% aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried ($MgSO_4$). Evaporation of the ether *in vacuo* at room temperature returned a green oil. The oil was taken up in a small volume of hexane and chromatographed on 45 g of silica gel. The column was eluted with 100 ml of hexane, then 300 ml of 5% ether in hexane. A distinctly yellow band separated and was collected. Evaporation of the solvent *in vacuo* gave 850 mg (58%) of the nitrosourethane as a yellow oil, homogeneous on tlc: ir 1870 (w), 1755 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.95 (6 H, t), 1.45 (5 H, m), 2.30 (4 H, t), 3.65 (2 H, d), 3.95 (3 H, s).

**$\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl Alcohol (9).**[4a]—A solution of 20.2 g (0.12 mol) of $\Delta^2$-2,3-dipropylcyclopropenecarboxylic acid[10] in 50 ml of dry ethyl ether was added dropwise over 1.5 hr to a stirred suspension of 8.8 g (0.24 mol) of $LiAlH_4$ in 100 ml of ether at −40°. The solution was stirred at −40° for 1 hr after the addition was complete, and then allowed to warm to room temperature and stirred for 2.5 hr. Excess hydride was destroyed by the dropwise addition of 5% aqueous NaOH. The white, granular precipitate was filtered off and extracted with 100 ml of boiling ether. The combined ether layers were washed with 5% aqueous NaOH, water, and saturated aqueous NaCl. After drying ($MgSO_4$), the ether was removed *in vacuo*, leaving a faintly yellow oil. The oil was distilled to give 16.9 g (92%) of colorless alcohol: bp 74–75° (1.5 mm); ir 3360 (s), 1870 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.55 (5 H, m), 2.43 (4 H, t), 3.53 (2 H, d), 4.1 (1 H, bs).

**$\Delta^2$-2,3-Dipropylcyclopropenecarboxaldehyde (13).**—A solution of 6.2 g (0.04 mol) of $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl alcohol in 50 ml of methylene chloride was added to 62 g of dipyridine chromium trioxide complex (Collins reagent)[16] in 650 ml of methylene chloride. After stirring for 0.75 hr at room temperature the mixture was filtered and concentrated *in vacuo* to a black oil. The oil was taken up in 200 ml of ethyl ether and filtered through a short column of silica gel. The filtrate was concentrated *in vacuo* to a yellow oil. Distillation afforded 4.2 g (70%) of product: bp 80–83° (3.5 mm); ir 2770 (m), 2690 (m), 1895 (w), 1690 $cm^{-1}$ (s); nmr (neat) $\delta$ 0.97 (6 H, t), 1.53 (4 H, m), 2.12 (1 H, d) 2.65 (4 H, t), 8.75 (1 H, d). The compound rapidly turned yellow upon standing in air.

**Methyl ($\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl) Carbonate (6).**—To a solution of 2.31 g (15 mmol) of 9 and 5 ml of pyridine in 50 ml of benzene, cooled in an ice bath, was added over 20 min a solution of 5 ml of methyl chloroformate in 5 ml of benzene. After the addition was complete, the ice bath was removed and the mixture was stirred for an additional 30 min. The mixture was then poured into 100 ml of 5% aqueous HCl and the layers were separated. The benzene layer was washed with 10% aqueous $NaHCO_3$ and saturated aqueous NaCl. After drying ($MgSO_4$), the solution was concentrated *in vacuo* to an oil. Distillation of the oil through a 6-in. Pt gauze column gave 2.42 g (80%) of product: bp 50° (0.05 mm); ir 1870 (w), 1750 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.53 (5 H, m), 2.42 (4 H, t), 3.68 (3 H, s), 3.98 (2 H, d); mass spectrum *m/e* 212.

*Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.76; H, 9.61.

**Ethyl ($\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl) Carbonate (7).**—

(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 1180.

(25) T. L. Brown, D. W. Dicherhoof, and D. A. Bafus, *J. Amer. Chem. Soc.*, **84**, 1371 (1962).

(26) C. Ruechardt and H. Schwarzer, *Chem. Ber.*, **99**, 1871 (1966).

Using ethyl chloroformate, **7** was prepared in identical fashion as described above for the preparation of **6**. The product was obtained in 71% yield: bp 62–63° (0.5 mm); ir 1750 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.30 (3 H, t), 1.53 (5 H, m), 2.42 (4H, t), 4.03 (2 H, d), 4.20 (2 H, t), mass spectrum *m/e* 226.

**Methyl ($\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl) Ether.**—A solution of 1.54 g (10 mmol) of **9** in 30 ml of ether, cooled in a Dry Ice–isopropyl alcohol bath, was treated with a 1.8 *M* solution of methyllithium ether until gas evolution ceased. After the solution had warmed to room temperature, excess methyl iodide was added and the mixture was refluxed for 24 hr. After aqueous work-up, glpc at 160° showed a 70:30 mixture of two components. The components were collected by preparative glpc and the first was identified as the desired ether: ir 1860 (w), 1110 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.50 (5 H, m), 2.42 (4 H, t), 3.27 (2 H, d), 3.33 (3 H, s). The second component was identified as the starting alcohol.

**$\Delta^2$-2,3-Dipropylcyclopropenylcarbinyl Acetate (12).**[4a]—A solution of 250 mg (1.4 mmol) of **9** in 10 ml of pyridine was treated with 2 ml of acetic anhydride over 10 min. The solution was stirred for a few minutes and then poured into 50 ml of 5% aqueous HCl. The aqueous solution was extracted twice with 50 ml of ether. The combined ether extracts were washed with water and saturated aqueous NaCl. After drying ($MgSO_4$), the ether was removed *in vacuo* to give 230 mg of an oil, homogeneous on glpc: ir 1860 (w), 1740 $cm^{-1}$ (s); nmr ($CCl_4$) $\delta$ 0.97 (6 H, t), 1.52 (5 H, m), 1.90 (3 H, s), 2.35 (4 H, t), 3.80 (2 H, d).

**Methyl ($\Delta^2$-2,3-Dipropylcyclopropenyl) Ketone (14).**—Modifying the published procedure,[17] 32 ml of a 2.0 *M* solution of methyllithium in ether was added over 1 hr to an ice-cold solution of 5 g (30 mmol) of $\Delta^2$-2,3-dipropylcyclopropenecarboxylic acid in 30 ml of ether. After the addition was complete, the solution was stirred at 0° for 1 hr, then poured with stirring into 30 ml of cold water. The layers were separated and the ether solution was washed with 5% aqueous NaOH, water, and saturated aqueous NaCl. After drying ($MgSO_4$), the ether was removed *in vacuo*. Distillation of the remaining oil gave 4.1 g (83%) of colorless ketone, bp 50–51° (0.45 mm) [lit.[17] bp 63–64° (1.4 mm)], 2,4-DNP mp 147.5–148° (EtOH).

**Methyl ($\Delta^2$-2,3-Dipropylcyclopropenyl) Ketohydrazone (3).**—A solution of 1.4 g (8.5 mmol) of **14** and 1.3 g (40 mmol) of 85% hydrazine in 40 ml of methanol was stirred at room temperature for 48 hr. Methanol and most of the excess hydrazine were removed *in vacuo* at room temperature, leaving a faintly yellow oil. The oil was taken up in ether, washed with water and saturated aqueous NaCl, and dried ($MgSO_4$). Evaporation of the ether *in vacuo* left a colorless oil (1.5 g): ir 3360 (s), 3210 (m), 1880 (w), 1620 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 0.97 (6 H, t), 1.40 (3 H, s), 1.57 (4 H, m), 2.17 (1 H, s), 2.42 (4 H, t), 4.50 (2 H, bs). The hydrazone was used without further purification; it was stored in methylene chloride solution at −5°.

**Methyl ($\Delta^2$-2,3-Dipropylcyclopropenyl)carbinyl Acetate (15).**—A solution of 1.7 g (10 mmol) of **14** in 20 ml of ether was added over 0.25 hr to a suspension of 0.38 g (10 mmol) of $LiAlH_4$ in ether at −70°. After addition was complete the mixture was stirred for 1 hr at −70° and then for 2 hr at room temperature. Destruction of the excess $LiAlH_4$ with 5% aqueous NaOH, followed by the usual work-up, gave 1.4 g (84%) of colorless alcohol: ir 3400 (s), 1860 $cm^{-1}$ (w); nmr (neat) $\delta$ 0.95 (6 H, t), 1.08 (3 H, d), 1.53 (5 H, m), 2.42 (4 H, t), 3.53 (1 H, dq), 3.62 (1 H, bs).

Without further purification, 0.7 g of the alcohol was stirred overnight with 1 ml of acetic anhydride in 15 ml of pyridine. The solution was concentrated *in vacuo*, leaving a brown oil. Distillation of the oil through an 8-in spinning band column afforded 0.6 g (73%) of colorless acetate: bp 70–71° (2.1 mm); ir 1860 (w), 1740 $cm^{-1}$ (s); nmr (neat) $\delta$ 0.95 (6 H, t), 1.10 (3 H, d), 1.50 (5 H, m), 1.88 (3 H, s), 2.38 (4 H, t), 4.58 (1 H, dq).

**Attempted Thermal Decomposition of 2.**—A solution of 0.425 g of **2** in 30 ml of cyclohexane was refluxed for 24 hr. No gas evolution was detected. The solution was cooled and the cyclohexane was removed *in vacuo*. Nmr of the recovered material (0.410 g) indicated it to be essentially pure **2**.

**Potassium *tert*-Butoxide Decomposition of 2.**—A solution of 0.82 g (3.4 mmol) of **2** in 10 ml of ether was added to a cold (−30°) suspension of 0.78 g (7 mmol) of potassium *tert*-butoxide in ether. No gas evolution was detected. After the solution was stirred for 20 min, 5 ml of water was injected into the mixture, resulting in a vigorous evolution of gas. The layers were separated and the colorless ether layer was washed with saturated aqueous NaCl. After drying ($MgSO_4$) the solution was concentrated *in vacuo* to a pale yellow oil (0.89 g). Glpc of the oil (160°) showed components with retention times of 4 and 10 min, which were identified by Moss as 3-propyl-1,3,4-heptatriene and 2-propyl-3-methyl-2-hexenal, respectively. No peaks with a longer retention time were observed.

**Lithium Ethoxide Decomposition of 2.**—To a stirred suspension of 0.42 g (8 mmol) of anhydrous lithium ethoxide in 30 ml of ether was rapidly added 0.97 g (4 mmol) of **2** in 20 ml of ether. A gradual evolution of 68 ml (75%) of $N_2$ occurred over 0.5 hr accompanied by fading of the yellow nitrosourethane color. After the solution was stirred for 3 hr at room temperature, 10 ml of water was added. The layers were separated and the ether layer was washed with saturated aqueous NaCl. After drying ($MgSO_4$), the ether solution was concentrated *in vacuo* to a brown oil (0.67 g). Nmr of the oil showed no trace of the starting nitrosourethane (absence of singlet at 3.95 ppm).

The oil was chromatographed on 20 g of silica gel. Progress of the chromatograph was monitored by glpc (160°). Elution with hexane (100 ml) afforded 30 mg (5%) of an oil with glpc retention time of 4 min. Its nmr and ir spectra were comparable with the data reported for 3-propyl-1,3,4-heptatriene.[4a]

Elution with 5% ether in hexane (250 ml) afforded 380 mg of an oil. Glpc showed it to be a mixture of two major components in a 2:3 ratio with retention times of 22 and 32.5 min, respectively, plus trace amounts of two overlapping peaks (9 and 10 min). The major components were isolated by preparative glpc and identified as the methyl carbonate **6** and the ethyl carbonate **7** by comparison of their spectral properties with those of authentic samples. The two trace components had the retention times of $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl alcohol (**9**) and *cis*- and *trans*-2-propyl-3-methyl-2-hexenal (**5**). Nmr of the components collected together showed aldehyde protons at 10.00 and 10.08 ppm and a doublet at 3.53 ppm characteristic of **9**. Treatment of the mixture with 2,4-DNP reagent afforded a derivative, mp 144–150° ($CH_3OH$).

Continued elution of the column with 500 ml of ether afforded 170 mg (25%) of a single component oil (glpc retention time 36.5 min) identified as 3,4-dipropylpyridazine (**8**): ir 3050 (w), 1580 (m), 1560 $cm^{-1}$ (m); nmr ($CDCl_3$) $\delta$ 1.03 (6 H, t), 1.72 (4 H, m), 2.67 (2 H, t), 3.00 (2 H, t), 7.27 (1 H, d, $J$ = 5.2 Hz), 8.92 (1 H, d, $J$ = 5.2 Hz); mass spectrum *m/e* 164, 136; uv $\lambda_{max}^{pentane}$ 254 m$\mu$ (log $\epsilon$ 2.9), 258 (2.9), 334 (2.2). Preparative glpc afforded an analytical sample.

*Anal.* Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.83; N, 17.05. Found: C, 73.15; H, 9.85; N, 16.95.

**Reaction of 6 with Lithium Ethoxide.**—A solution of **6** (100 mg) and lithium ethoxide (100 mg) in ether (20 ml) was stirred at room temperature for 3 hr. The reaction was quenched with 20 ml of water and the layers were separated. Glpc of the ether solution revealed virtually complete conversion of **6** to a mixture of the ethyl carbonate **7** (85%) and alcohol **9** (15%).

**Sodium Ethoxide Decomposition of 2. A.**—A solution of 2.1 g (9 mmol) of **2** and 2 drops of methanol in 30 ml of ether was rapidly added to a stirred suspension of 1.2 g (22 mmol) of anhydrous sodium methoxide in 20 ml of ether. Within 5 min, 105 ml (52%) of gas was collected and the solution turned a faint pink. After the solution was stirred for 4 hr at room temperature, the pink color had faded with little further gas evolution. An aliquot of the mixture was removed and examined by glpc (80°) for the presence of 4-octyne and dimethyl carbonate. By comparing the glpc traces of the reaction mixture and appropriate calibration mixtures, the yields of 4-octyne (<1.4%) and dimethyl carbonate (12%) could be estimated.

The rest of the mixture was quenched with 20 ml of water. After the mixture was stirred for a few minutes, the layers were separated and the organic layer was washed with saturated aqueous NaCl. After drying ($MgSO_4$), the ether solution was concentrated *in vacuo* to a brown oil (1.4 g). Nmr of the oil showed no trace of **2** (absence of 3 H singlet at 3.95 ppm). Glpc of the mixture (160°) showed a mixture of *ca.* ten products; addition of small amounts of methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl) ether to the reaction mixture followed by glpc demonstrated that none of the peaks corresponded to the ether.

The mixture was chromatographed on 40 g of silica gel as described above. Elution with hexane afforded 60 mg (5%) of 3-propyl-1,3,4-heptatriene (**4**). Elution with 20% ether in hexane afforded 710 mg of oil containing six minor compounds

(60%) (glpc retention times of 4.5–14 min) and one major component (40%) (time 22 min). Isolation by preparative glpc afforded the major component methyl ($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl) carbonate **6**. Two of the minor components were identified as $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl alcohol (**9**) and *cis*- and *trans*-2-propyl-3-methyl-2-hexenal (**5**) as described above. Elution with ether then afforded 200 mg (15%) of 3,4-dipropylpyridazine (**8**).

**B.**—A 5-min-old slurry of 200 mg (3.7 mmol) of sodium methoxide, 425 mg (1.7 mmol) of **2**, and 1 drop of methanol in 30 ml of ether was quenched by the addition of 4 ml of glacial acetic acid, resulting in vigorous gas evolution. The mixture was poured into 50 ml of water and the layers were separated. The ether layer was washed with water, 10% aqueous $NaHCO_3$, and saturated aqueous NaCl. After drying ($MgSO_4$), the solution was concentrated *in vacuo* to an oil (300 mg). Nmr showed no absorption at 3.95 ppm. Molecular distillation of the oil at 100° (0.05 mm) left no residue. Glpc (160°) showed a group of seven peaks with retention times of 4 to 14 min (38%), and two major peaks with retention times of 15.5 (38%) and 22 min (24%) (percentage by disk integration of peak areas). The peak with retention time of 22 min corresponded to the methyl carbonate **6**; none of the pyridazine **8** (retention time 36.5 min) could be detected. The peak with a retention time of 15.5 min was collected by preparative glpc and identified as $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl acetate (**12**) by spectral comparison with an authentic sample.

By comparison, a mixture of 1.14 g (4.8 mmol) of **2** and 0.59 g (11 mmol) of $NaOCH_3$ when decomposed as in part A afforded only 0.4 g of oil when subjected to molecular distillation at 100° (0.05 mm), leaving *ca.* 100 mg of nonvolatile residue which showed an infrared band at 1640 $cm^{-1}$. Glpc of the oil (160°) showed the group of seven peaks with retention times of 4 to 14 min (33%), and peaks with retention times of 22 (27%) and 36.5 min (20%). The latter two corresponded to the previously identified methyl carbonate **6** and pyridazine **8**. (Glpc percentages total 80%; the remaining 20% of the reaction mixture is the nonvolatile material removed by distillation.)

**C.**—A 5-min-old slurry of 270 mg (5 mmol) of sodium methoxide, 600 mg (2.5 mmol) of **2**, and 1 drop of methanol in 10 ml of ether was filtered in an inert atmosphere. An aliquot of the pink filtrate was transferred *via* syringe to an infrared cell. The infrared spectrum showed a strong diazo band at 2040 $cm^{-1}$.

**Reaction of 6 with Sodium Methoxide.**—A solution of 200 mg of **6** in 10 ml of ether was treated with 600 mg of sodium methoxide. After the solution was stirred for 3.5 hr at room temperature, 10 ml of water was added and the layers were separated. The ether layer was washed with saturated aqueous NaCl and dried ($MgSO_4$). Glpc (160°) showed a mixture of 15% of $\Delta^2$-2,3-dipropylcyclopropenylcarbinyl alcohol and 85% of **6**.

**Lead Tetraacetate Oxidation of 3.**—A solution of 2.7 g (15 mmol) of **3** in 40 ml of methylene chloride was added over 1.5 hr to an ice-cold solution of 9.8 g (22 mmol) of lead tetraacetate in 80 ml of methylene chloride. Nitrogen evolution was evident during the addition and a white precipitate of lead acetate formed. After the addition was complete, the mixture was allowed to warm to room temperature for 0.5 hr. The mixture was poured into 30 ml of water and the layers were separated. The organic phase was washed with 10% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo* to an oil (3.3 g). The oil (2 g) was chromatographed on 30 g of silica gel. Elution with hexane (100 ml) afforded 0.197 g of an unidentified unsaturated acetate, ir 3040 (m), 1740 (s), 1630 $cm^{-1}$ (w), no cyclopropene C=C. Elution with 25% ether in hexane afforded 1.0 g (51%) of methyl ($\Delta^2$-2,3-dipropylcyclopropenyl)carbinyl acetate (**15**), identical with an authentic sample.

**Mercuric Oxide Oxidation of 3.**—A solution of 2.3 g (13 mmol) of **3** in 20 ml of petroleum ether (bp 30–60°) was added over 10 min to a suspension of 6.1 g (26 mmol) of mercuric oxide (yellow powder) in 200 ml of petroleum ether. The mixture was stirred at high speed in a 500-ml Morton flask at room temperature for 24 hr.

The mixture was filtered through a bed of $MgSO_4$ and the filtrate was concentrated *in vacuo* to a brown oil (2.2 g). The oil was chromatographed on 50 g of silica gel. Elution with 600 ml of 1:3 ether–hexane afforded a dark multicomponent oil which was not investigated further. Elution with 450 ml of 3:1 ether–hexane afforded 1.35 g (58%) of a single-component oil by glpc, identified as 3,4-dipropyl-6-methylpyridazine (**17**): ir 3030 (w), 1590 (s), 1540 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 1.00 (6 H, t), 1.78 (4 H, m), 2.58 (2 H, t), 2.62 (3 H, s), 2.95 (2 H, t), 7.10 (1 H, s); uv $\lambda_{max}^{pet\ ether}$ 262 m$\mu$ (log $\epsilon$ 3.3), 334 (2.5); mass spectrum *m/e* 178, 163, 150, 135. An analytical sample was obtained by preparative glpc as a colorless oil.

*Anal.* Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18. Found: C, 74.30; H, 10.26.

**Thermal Stability of 3.**—A solution of **3** (0.7 g) in 50 ml of absolute ethanol was refluxed for 18 hr. The ethanol was removed *in vacuo* at room temperature. The nmr and ir spectra of the residue were identical with those from freshly prepared **3**.

A solution of **3** (150 mg) in 0.5 ml of $CDCl_3$ was placed in a sealed nmr tube. The nmr spectrum showed an 18:2 integral ratio of CH ($\delta$ 0.95–2.42) to NH protons ($\delta$ 4.50). After 24 hr at room temperature the ratio was 18:1.3, consistent with gradual azine formation. No changes were observed in the CH portion of the spectrum.

**Registry No.**—**2**, 35890-03-0; **6**, 35890-04-1; **7**, 35890-05-2; **8**, 35890-06-3; **9**, 35890-07-4; **13**, 35890-08-5; **15**, 35890-09-6; **17**, 35890-10-9; 1-cyano-2,3-dipropylcycloprop-2-ene, 7525-49-7; $\Delta^2$-2,3-dipropylcyclopropenylcarbinylamine, 35890-12-1; $\Delta^2$-2,3-dipropylcyclopropenylcarbinylamine hydrochloride, 35890-13-2; methyl *N*-($\Delta^2$-2,3-dipropylcyclopropenylcarbinyl)urethane, 7572-55-6.

**Acknowledgment.**—Acknowledgment is made to the Research Corporation for partial support of this work.

# Photolysis of Phenyl- and Diphenyldiazomethanes in Alkyl and Allylic Sulfides

WATARU ANDO,* MICHIO YAMADA, EIICHI MATSUZAKI, AND TOSHIHIKO MIGITA

*Department of Chemistry, Gunma University, Kiryu, Gunma, Japan*

*Received April 14, 1972*

Photolysis of phenyl- and diphenyldiazomethanes in dimethyl sulfide gives ortho-substituted sulfur compounds through the sulfonium ylide intermediate. Photodecomposition of phenyldiazomethane in benzyl methyl sulfide gives the insertion product of phenylcarbene into benzyl hydrogen, presumably by ylide rearrangement of the benzyl group. The reaction in allylic sulfides gave allyl(alkylthio)arylmethanes together with some cyclopropane derivatives. Thermal decomposition of phenyldiazomethane gives only addition product, but diphenyldiazomethane gives both addition and insertion products.

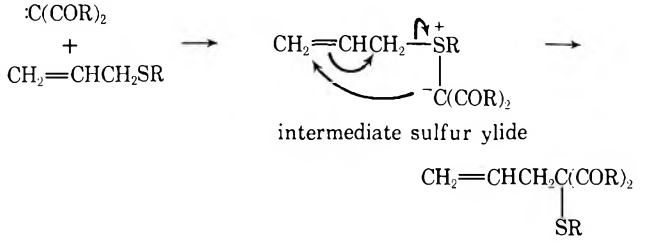
Dialkyl sulfides give stable sulfur ylides by addition of singlet carbenes containing strongly electron-withdrawing substituents. Bis(phenylsulfonyl)carbene could be trapped with di-*n*-butyl sulfide to give the ylide.[1] The photoinduced reaction of diazo biscar-

(1) J. Diekmann, *J. Org. Chem.*, **28**, 2933 (1963); **30**, 2272 (1965).

bonyl compounds with dimethyl sulfide also produced stable sulfur ylides.[2-4]

$$N_2C(COR)_2 + CH_3SCH_3 \xrightarrow{h\nu} (CH_3)_2\overset{+}{S}\overset{-}{C}(COR)_2$$
$$R = OCH_3, OC_2H_5, CH_3$$

However, in the reaction with allylic sulfides, the sulfonium ylide was not isolated and insertion of the carbene into the C–S bond was found to be important. The rationalization is the familiar one in which the insertion of electrophilic singlet carbene takes place in two steps: the formation of sulfonium ylide followed by the 2,3-sigmatropic rearrangement.[5-7]




intermediate sulfur ylide



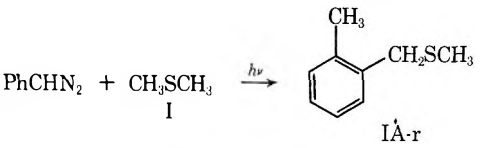

These approaches have been applied successfully on occasion in carbonylcarbene reactions, but little is known about the behavior of arylcarbenes in sulfur compounds. In this paper, we report the electrophilic reactions of phenyl- and diphenylcarbenes on sulfur compounds and the results are compared with those of sulfonium salts.

## Results

Photochemical decomposition of phenyl- and diphenyldiazomethanes in a 20-mol excess of alkyl sulfide was carried out in Pyrex vessels, without degassing, using a Rikosha 400-W high-pressure mercury lamp. Photolysis was generally complete, as indicated by disappearance of the diazo band at 2040 $cm^{-1}$ in the infrared spectrum. Products were identified by glpc retention time, ir, nmr, and elemental analysis.

**Reactions of Phenyldiazomethane in Aliphatic Sulfides and Disulfides.**—The photolysis of phenyldiazomethane in dimethyl sulfide was performed at room temperature. The sulfur ylide might be expected to form by electrophilic attack of singlet phenylcarbene on the sulfur atom. No more than a trace of sulfonium ylide could be observed from the analysis of the nmr spectrum of the reaction mixture. Product analysis by glpc showed the presence of *o*-methylbenzylmethyl sulfide (IA-r) in 20% yield; the structure was established by comparison with an authentic sample.[8] Stilbene and benzalazine were observed in 6 and 10% yields, respectively.

On the other hand, the reaction in diethyl and benzyl methyl sulfides gave the insertion products of phenylcarbene into the α-C–H bond. Reactions in diiso-




propyl and di-*tert*-butyl sulfides gave the olefin elimination products as major product.

$$PhCHN_2 + RSR^1 \xrightarrow{h\nu} \underset{\text{α-C–H insertion (A-In)}}{RSCHR'} + \underset{\text{elimination (E)}}{RSCH_2Ph}$$
$$CH_2Ph$$

II, R = $R^1$ = $C_2H_5$
III, R = $R^1$ = *i*-$C_3H_7$
IV, R = $R^1$ = *t*-$C_4H_9$
V, R = $C_2H_5$; $R^1$ = *t*-$C_4H_9$
VI, R = Ph; $R^1$ = $C_2H_5$

VII, R = $CH_3$; $R^1$ = $PhCH_2$
VIII, R = $C_2H_5$; $R^1$ = $PhCH_2$
IX, R = $CH_3$; $R^1$ = $SCH_3$
X, R = $C_2H_5$; $R^1$ = $SC_2H_5$

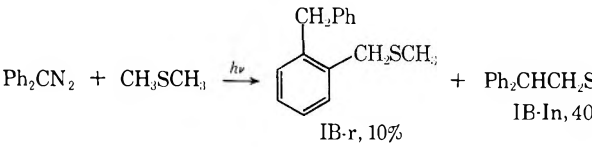
In these reactions, benzaldehyde, benzalazine, and *cis*- and *trans*-stilbene were also obtained as major products (total yields of these products were approximately 30%).

The photolysis of phenyldiazomethane in dimethyl and diethyl disulfide gave as the principal products methyl benzyl sulfide (IA-E) in 15% yield and ethyl benzyl sulfide (IIA-E) in 17% yield, respectively (Table I).

TABLE I
YIELDS OF PRODUCTS FROM THE PHOTOLYSIS OF PHENYLDIAZOMETHANE IN ALIPHATIC SULFIDES AND DISULFIDES

| Sulfide | Elimination (= A-E), % | Insertion (= A-In), % |
|---|---|---|
| II | 4 | 35 |
| III | 29 | 0 |
| IV | 25 | 0 |
| V | 21 (IIA-E) | 0 |
| VI | 19 | Trace |
| VII | 0 | 20 |
| VIII | 3 | 22 |
| IX | 15 (IA-E) | 0 |
| X | 17 (IIA-E) | 0 |

**Photolysis of Diphenyldiazomethane in Aliphatic Sulfides and Disulfides.**—The photolysis of diphenyldiazomethane in alkyl sulfides and disulfides was carried out in Pyrex vessels without degassing. The crude reaction mixture in dimethyl sulfide showed an nmr signal at 2.10 ppm (singlet) in chloroform, which might be assigned to the proton signal of $CH_3SCH_3^+$, but the corresponding sulfonium ylide could not be isolated by thin layer chromatography. Glpc analysis showed the formation of *o*-benzylbenzylmethyl sulfide (IB-r) and 1,1-diphenyl-2-methylthioethane (IB-In) in 10 and 40% yields, respectively. The structures of these products were determined by elemental and spectral analyses. Diphenylazine and benzophenone (about 10% each) were minor products.




An analogous α-C–H insertion product (IIB-In) was also observed together with some elimination product (IIB-E) when the photolysis of dihenyldiazomethane

(2) W. Ando, T. Yagihara, S. Tozune, and T. Migita, *J. Amer. Chem. Soc.*, **91**, 2786 (1969).
(3) W. Ando, T. Yagihara, S. Tozune, S. Nakaido, and T. Migita, *Tetrahedron Lett.*, 1979 (1969).
(4) W. Ando, T. Yagihara, and T. Migita, *ibid.*, 1983 (1969).
(5) W. Ando, K. Nakayama, K. Ichibori, and T. Migita, *J. Amer. Chem. Soc.*, **91**, 5164 (1969).
(6) W. Ando, S. Kondo, and T. Migita, *ibid.*, **91**, 6516 (1969).
(7) W. Ando, S. Kondo, K. Nakayama, K. Ichibori, K. Kohda, H. Yamato, I. Imai, S. Nakaido, and T. Migita, *ibid.*, **94**, 3870 (1972).
(8) M. Yoshimine and M. J. Hatch, *ibid.*, **89**, 5831 (1967).

was carried out in diethyl sulfide. On the other hand, in diisopropyl sulfide, two major products, isopropylbenzhydryl sulfide (IIIB-E) and isopropyl(isopropylthio)diphenylmethane (IIIB-In), were obtained in 20 and 15% yields, respectively.

$$Ph_2CN_2 + C_2H_5SC_2H_5 \xrightarrow{h\nu} \underset{\text{IIB-E}}{C_2H_5SCHPh_2} + \underset{\text{IIB-In}}{C_2H_5SCHCH_3\,(CHPh_2)}$$

$$Ph_2CN_2 + (CH_3)_2CHSCH(CH_3)_2 \xrightarrow{h\nu} \underset{\text{IIIB-E}}{(CH_3)_2CHSCHPh_2} + \underset{\text{IIIB-In}}{(CH_3)_2CHSCPh_2CH(CH_3)_2}$$

Product IIIB-In was identified as the insertion product of diphenylcarbene into the C–S bond. Its nmr spectrum showed two isopropyl groups as a doublet at 0.82 and 0.87 ppm. This product was synthesized independently from the reaction of isopropyl diphenylcarbinol and isopropyl mercaptan.[9] Product IIIB-E was found to be the elimination product identical with that found in the reaction of diphenyldiazomethane with isopropyl mercaptan.

Similar elimination products were also found in the reactions of diphenyldiazomethane with dimethyl- and diethyl disulfide. Reaction in dimethyl disulfide gave methyl benzhydryl sulfide IB-E in 49% yield; in diethyl disulfide, ethyl benzhydryl sulfide IIB-E in 28% yield was formed together with 1,1-diphenylpropene (XI) in 21% yield.

$$Ph_2CN_2 + RSSR \xrightarrow{h\nu} \underset{R = CH_3,\ C_2H_5}{RSCHPh_2} + \underset{\text{XI}}{Ph_2C{=}CHCH_3}$$

**Solvent Effects on the Reaction of Diphenyldiazomethane in Dimethyl Sulfide.**—Photolyses of diphenyldiazomethane in dimethyl sulfide, diluted with an inert solvent such as benzene, cyclohexane, acetone, or mesityl oxide, were also done at room temperature without degassing. Use of purified cyclohexane or benzene (mole fraction 0.5) as diluent gave no change in the ratio of IB-r/IB-In, 0.3–0.4. This is to be compared with 0.25 in pure dimethyl sulfide. A control experiment showed that diluted solvents were not reacting with diphenyldiazomethane. A similar experiment was carried out using a mixture of dimethyl sulfide and acetone or mesityl oxide (mole fraction 0.5). Photolysis for 2.5 hr, followed by work-up and analysis by gas chromatography, gave the ratio of IB-r/IB-In of 3–3.5. It is clear that a major portion of the reaction product was apparently affected by solvent (Table II).

**Reactions of Dialkylbenzhydrylsulfonium Salts.**—Similar rearrangement and insertion products are observed with sulfonium salts. Dimethylbenzhydrylsulfonium bromide was prepared in low yield using diphenylbromomethane and dimethyl sulfide. The salt, though crystalline, was highly hygroscopic and the corresponding fluoroborate salt XII was therefore prepared. Sodium amide was added to a slurry of XII in acetone. However, IB-r was formed as major product together with trace of IB-In. In dimethyl sulfide, IB-r was also obtained as major product, but IB-In was formed in 5% yield. Alkylation of diethyl sulfide by diphenylbromomethane generated the crystalline sulfonium salt XIII; sodium amide converted the salt exclusively to rearrangement product XIIIB-r. However, none of IIB-In could be detected in acetone or benzene solvents. We attempted to prepare compound XIV using bromide, diisopropyl sulfide, and silver perchlorate. Addition of sodium amide to a benzene or acetone slurry of XIV afforded product IIIB-E and IIIB-In in comparable yields, as determined by vpc analysis. These results are compared with those obtained in the reaction of diphenyldiazomethane with alkyl sulfides.

(9) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 84 (1949).

TABLE II

SOLVENT EFFECTS ON THE REACTION OF DIPHENYLDIAZOMETHANE WITH DIMETHYL SULFIDE

| Solvent | Mole ratio (sulfide/solvent) | Product ratio (IB-r/IB-In) |
|---|---|---|
| Cyclohexane | 3.3 | 0.2 |
| | 0.5 | 0.3 |
| Benzene | 0.3 | 0.3 |
| | 3.5 | 0.4 |
| Acetone | 0.3 | 3.2 |
| | 0.5 | 2.8 |
| Mesityl oxide | 0.3 | 3.5 |
| | 0.5 | 3.5 |

$$Ph_2CHS^+(CH_3)(CH_3) \xrightarrow{NaNH_2} \text{IB-r} + \text{IB-In}$$

XII

In acetone: IB-r 55%, IB-In 0%

In $CH_3SCH_3$: IB-r 31%, IB-In 5%

$$Ph_2CHS^+(C_2H_5)_2 \xrightarrow{NaNH_2} \text{IIB-E} + \text{XIIIB-r}$$

XIII

XIIIB-r = $CH_2Ph$ / $CH(Me)SC_2H_5$

In acetone: Trace, 45%

In benzene: 9%, 64%

$$Ph_2CHS^+(i\text{-}C_3H_7)(i\text{-}C_3H_7) \xrightarrow[\text{benzene}]{NaNH_2} \text{IIIB-In} + \text{IIIB-E}$$

XIV

IIIB-In 22%, IIIB-E 23%

**Reactions of Phenyl- and Diphenyldiazomethanes in Allylic Sulfides.**—Thermal and photolytical decomposition of phenyl- and diphenyldiazomethanes produced insertion and addition products (Table III).

TABLE III

YIELDS OF PRODUCTS IN THE REACTION OF PHENYL- AND DIPHENYLDIAZOMETHANES IN ALLYLIC SULFIDES

| | | Sulfide | | | Insertion (i), % | | | Addition (a), % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | R | $R^1$ | $R^2$ | $R^3$ | *a* | *b* | *c* | *a* | *b* | *c* |
| XV | H | $C_2H_5$ | H | H | 0 | 49 | 31 | 29 | 0 | 4 |
| XVI | H | $C_2N_5$ | H | $CH_3$ | 0 | 45 | 30 | 0 | 0 | 0 |
| XVII | H | *t*-Bu | H | H | 0 | 54 | 29 | 28 | 0 | 6 |
| XVIII | Ph | $C_2H_5$ | H | H | 26 | 38 | 26 | 20 | 3 | 0 |
| XIX | Ph | $C_2H_5$ | $CH_3$ | H | 15 | 43 | 21 | 7 | 0 | 0 |
| XX | Ph | $C_2H_5$ | H | $CH_3$ | 18 | 26 | 36 | 0 | 0 | 0 |
| XXI | Ph | *t*-Bu | H | H | 6 | 14 | 22 | 17 | 16 | 3 |

[a] Thermal decomposition at 110–140°. [b] Cupric sulfate catalyzed thermal decomposition at 110°. [c] Photolysis.

The photolysis of phenyldiazomethane in allyl sulfide afforded the principal product XV-i in 31% yield and the minor product XV-a in 4% yield. A control experiment demonstrated that these products were

not altered by reaction and work-up conditions. The product XV-i was found to be an insertion product of phenylcarbene into the allyl carbon–sulfur bond and XV-a to be an addition product of phenylcarbene to the C=C bond. The structures of these products were determined by elemental analysis and the examination of nmr and ir spectra. The reaction of phenyldiazomethane with γ-methylallyl ethyl sulfide gave XVI-i in 30% yield, which was identified as α-(1-methyl-2-propenyl)-α-ethylthiophenylmethane by spectral analyses. There was no trace of any isomer such as α-(2-butenyl)-α-ethylthiophenylmethane in the reaction products.[10] Insertion product XV-i was also

$$N_2CRPh + R^3CH{=}CR^2CH_2SR^1 \xrightarrow{h\nu} CH_2{=}CR^2CHR^3CRSR^1 + R^3CHCR^2CH_2SR^1$$

(Ph: insertion (i); CRPh: addition (a))

obtained in 49% yield when phenyldiazomethane was decomposed at 110° in the presence of cupric sulfate. No addition product was obtained. On the other hand, the thermolysis of phenyldiazomethane in allyl sulfide at 140° afforded XV-a in 29% yield, and C–S bond insertion product was not detected.

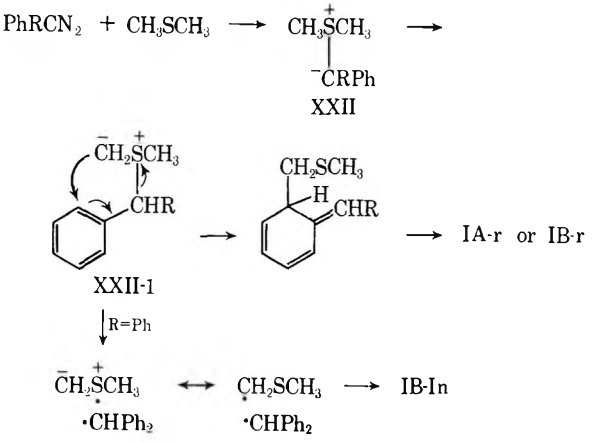
Similarly, in the thermolysis of diphenyldiazomethane without catalysis both addition and insertion products were obtained in comparable yields. On the other hand, the thermolysis and photolysis afforded the insertion product as major product.

## Discussion

To date there is no concrete evidence that aryl-substituted sulfur ylides are formed in the reaction of aryldiazomethane with alkyl sulfides, although the photolysis of phenyl- and diphenyldiazomethane in benzyl methyl sulfide has been reported.[11] Relatively little is known about the isolation of stable onium ylide in the reaction of diazo compounds with heteroatoms.[1-3,12] The formation of onium ylides is explained as the electrophilic attack of singlet carbene on the nonbonding electron pair of the heteroatom.

In contrast to bis(carbomethoxy)carbene, which reacts with a number of alkyl sulfides to give stable ylides,[2,3] phenyl- and diphenylcarbene did not, but afforded the products which are considered to be produced by further reaction of the corresponding ylides.

It is possible that when phenyl- and diphenylcarbene react with sulfur atom to form the unstable sulfonium ylides, the Sommelet–Hauser and Stevens rearrangements products could be responsible for either sulfur ylides.[13] Thus, the formation of ortho-substituted products, IA-r and IB-r, involves presumably the rearrangement of an intermediate sulfonium ylide XXII in which less predominant ylide XXII-1 is the reactive intermediate and the benzene ring functions as an acceptor, similar to that proposed for the analogous rearrangement of sulfonium ion.[13] The Stevens 1,2-shift product, IB-In, probably arises from the intermediate XXII–1 with radical pair as suggested by other workers.[14-18] Analogous product was also obtained in the reaction of sulfonium salt, although the Sommelet–Hauser process predominates.




The insertion products of phenyl- and diphenylcarbene into α-C–H bond are the expected Stevens 1,2-shift products from the corresponding sulfonium ylides. Although the Stevens shifts have been reported in the reaction of dibenzylmethyl sulfonium salt[19] together with the Sommelet–Hauser product, none of Stevens product was obtained in the reaction of XIII. This is not in accord with the fact that phenyl- and diphenylcarbene gave only Stevens product and none of Sommelet–Hauser product in the reaction with diethyl sulfide. It is not clear that α-C–H insertion products are formed, whether by the direct insertion of the carbene into α-C–H or the formation of sulfonium ylide followed by the Stevens rearrangement through the radical pair. However, since the basicity of the intermediate carbanion on the sulfur ylide is one of the important factors controlling the Stevens or Sommelet–Hauser rearrangement, and the weak bases predominate Stevens product,[19] it could be possible that the sulfur ylide formed by the reaction of phenyl- and diphenylcarbene gives predominantly the Stevens 1,2-shift products, but not by sulfonium ion.

Photolysis of phenyldiazomethane in diisopropyl and di-*tert*-butyl sulfides gave only isopropyl and *tert*-butyl benzyl sulfides. In these reactions, the Sommelet–Hauser and Stevens products were not formed. The mechanism of these reactions is considered to be the formation of sulfonium ylide intermediate followed by cis elimination through five-membered cyclic transition states.

In the reaction with dialkyl disulfides, the elimination product seems reasonable to formulate as the formation of sulfonium ylide by electrophilic attack of the phenylcarbene on the sulfur atom followed by a cyclic concerted process. Similar cleavage of the sulfur–sulfur bond has been observed in the reaction of bis(carbo-

(10) A control experiment showed that the γ-methylallyl ethyl sulfide, did not isomerize to α-methylallyl ethyl sulfide, which was only detected in less than 1% amount either before or after photolysis.

(11) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4675 (1952).

(12) D. Lloyd and M. I. Csinger, *Chem. Ind. (London)*, 118, 510, 787 (1967); *Chem. Commun.*, 1042 (1970).

(13) C. R. Hauser, S. W. Kantor, and W. R. Brasen, *J. Amer. Chem. Soc.*, **75**, 2660 (1953).

(14) U. Schollkopf, G. Ostermann, and J. Schossing, *Tetrahedron Lett.*, 2619 (1969).

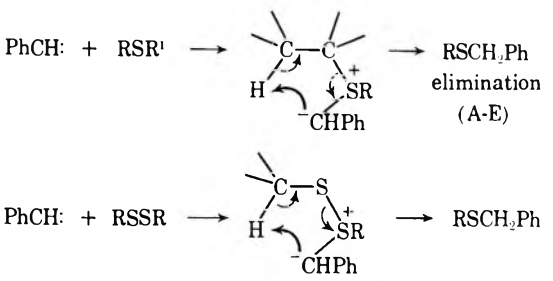
(15) A. R. Lepley, *J. Amer. Chem. Soc.*, **91**, 1237 (1969).

(16) R. W. Jemison and D. J. Morries, *Chem. Commun.*, 1226 (1969).

(17) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *ibid.*, 576 (1970).

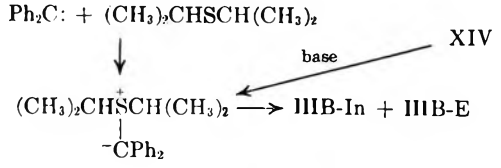
(18) A. R. Lepley, R. H. Beckler, and A. G. Ginmanini, *J. Org. Chem.*, **36**, 1222 (1971).

(19) Y. Hayashi and R. Oda, *Tetrahedron Lett.*, 5581 (1968).




methoxy)carbene with alkyl disulfides as principal pathway.[20]

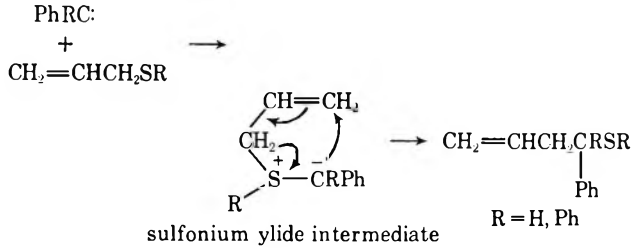
Photolysis of diphenyldiazomethane in diisopropyl sulfide also gave the elimination product together with the insertion product of diphenylcarbene into the C–S bond. The insertion of the carbene into the alkyl carbon–sulfur bond appears unusual and is considered to be analogous to that represented for the Stevens 1,2-shift of intermediate sulfonium ylide, in which the isopropyl group probably migrated from the sulfonium center to an adjacent carbanionic carbon. This mechanism is supported by the formation of analogous Stevens and the elimination products in the reaction of sulfonium salt XIV with sodium amide in benzene or acetone.




Accordingly, under the photolytic conditions, the phenyl and diphenylcarbenes could interact with sulfur atom to give either the Sommelet–Hauser, Stevens 1,2-shift, or β-elimination product, depending on the nature of the intermediate carbanion.

The formation of rearranged insertion products in the reactions of the carbene with allylic sulfides is also explained in terms of the ylide mechanism, as has been suggested in the similar reactions of carbonylcarbenes.[5-7]

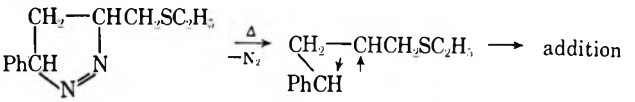
The phenyl- and diphenylcarbenes or carbenoids generated in the photolysis or the copper sulfate thermal reaction convert the sulfide to sulfonium ylide followed by allylic 2,3-sigmatropic rearrangement, but do not convert the olefin to cyclopropane, showing little reactivity in comparison with sulfur atom.



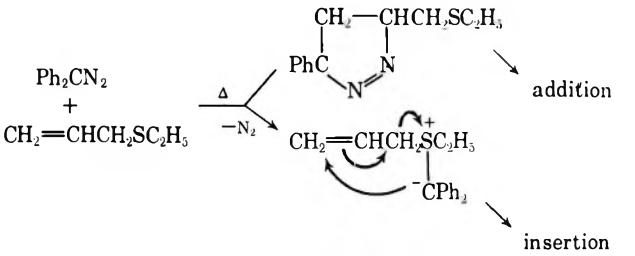

The thermal reaction of phenyl- and diphenyldiazomethanes (reaction conditions a) is also a reaction in which involvement of carbene is often assumed, and, as mentioned above, the sulfonium ylide intermediate was readily rationalized as resulting from attack of the carbene.

(20) W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, **37**, 1721 (1972).

However, the thermolysis of phenyldiazomethane in allyl sulfide at 140° afforded the product XV-a in 29% yield, and none of the C–S bond insertion product of the carbene was detected. It is now evident that the addition process is favored over the insertion process. Interpreting these reactions, the formation of addition product occurs not in carbene reactions, but in the addition of diazo compound itself on the C=C bond to form pyrazoline followed by loss of nitrogen and the formation of singlet diradical in which ring closure must occur. The phenylcarbene is not produced under the reaction conditions.




In the thermolysis of diphenyldiazomethane in allyl sulfide, both addition and insertion products were obtained in comparable yields, and in γ- or β-methylallyl sulfides, the insertion product was obtained as the only major product. These data indicate that the cyclopropane formation probably arises from the pyrazoline intermediate and the insertion product from the sulfonium ylide intermediate.




Under the reaction conditions, the diphenyldiazomethane could either decompose to produce the carbene or react with olefin to form the pyrazoline. The steric factor is most important for the pyrazoline formation giving the cyclopropane.

## Experimental Section

**Instruments.**—Ir spectra were recorded on a Japan Spectroscopic Co. DS-21 spectrometer. Nmr spectra were recorded on a Varian A-60D spectrometer in $CCl_4$ solutions with an internal $(CH_3)_4Si$ standard. Gas–liquid partition chromatography (glpc) was used extensively for the separation and purification of products and for yield determinations. The internal standard method was used in yield determination. The glpc column used included 10% Carbowax 20M, 2 ft × 0.25 in. on Celite 22; 10% SF-96, 4 ft × 0.25 in. on Celite 545; and 5% SE-30, 4 ft × 0.25 in. on Celite 22.

**Materials.**—The reagents dimethyl, diethyl, and di-*tert*-butyl sulfides and dimethyl, diethyl, and diisopropyl disulfides were obtained commercially and purified by distillation before use. Benzyl methyl sulfide,[21] ethyl *tert*-butyl sulfide,[21] phenyl ethyl and phenyl isopropyl sulfides,[22] and allylic sulfides[23] were prepared by known procedure as referenced. Phenyldiazomethane was prepared by the action of sodium methoxide on benzaldehyde tosylhydrazine.[24] Diphenyldiazomethane was prepared by the oxidation of benzophenone hydrazone with yellow mercuric oxide.[25]

**Synthesis of Benzhydryldimethylsulfonium Fluoroborate (XII).**

(21) W. Windus and P. R. Shildneck, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 345.
(22) A. Vogel, *J. Chem. Soc.*, 1822 (1948).
(23) D. S. Tarbell and W. F. Lovett, *J. Amer. Chem. Soc.*, **78**, 2259 (1956).
(24) R. A. Moss and U. H. Dolling, *ibid.*, **93**, 954 (1971).
(25) L. I. Smith and K. L. Howard, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 351.

TABLE IV

NMR DATA FOR ARYLSULFUR COMPOUNDS[a]

IB-r: 1.90 (s, 3 H), 3.53 (s, 2 H), 4.11 (s, 2 H), 6.88–7.38 (m, 9 H). IB-In: 1.94 (s, 3 H), 3.08 (d, 2 H), 4.12 (t, 1 H), 6.85–7.40 (m, 10 H). IIA-In: 1.18 (d, 3 H), 1.23 (t, 3 H), 2.48 (q, 2 H), 2.89 (m, 3 H), 7.15 (s, 5 H). IIB-In: 1.15 (t, 3 H), 1.27 (d, 3 H), 2.30 (q, 2 H), 3.4–4.1 (m, 2 H), 6.9–7.4 (m, 10 H). IIIB-In: 0.82 (d, 6 H), 0.87 (d, 6 H), 1.97–2.42 (m, 1 H), 2.69–3.20 (m, 1 H), 7.06–7.52 (m, 10 H). IIIB-E: 1.24 (d, 6 H), 2.34–2.88 (m, 1 H), 5.13 (s, 1 H), 6.92–7.56 (m, 10 H). VIIA-In: 1.77 (s, 3 H), 3.06 (m, 2 H), 3.72 (m, 1 H), 7.09 (m, 10 H). XIIIB-r: 1.03 (t, 3 H), 1.33 (d, 3 H), 2.18 (q, 2 H), 4.06 (s, 2 H), 4.16 (m, 1 H), 6.9–7.6 (m, 9 H). XV-i: 1.11 (t, 3 H), 2.23 (q, 2 H), 2.55 (t, 2 H), 3.77 (t, 1 H), 4.95 (m, 2 H), 5.63 (m, 1 H), 7.22 (s, 5 H). XV-a: 0.8–1.2 (m, 2 H), 1.22 (t, 3 H), 1.5–2.0 (m, 1 H), 2.53 (d, + q, 4 H), 7.06 (m, 5 H). XVI-i: 0.96–1.13 (t + d, 6 H), 2.33 (m, 3 H), 3.62 (d, 1 H), 4.94 (m, 2 H), 5.62 (m, 1 H), 7.18 (s, 5 H). XVII-i: 1.14 (s, 9 H), 2.48 (t, 2 H), 3.79 (t, 1 H), 4.39 (m, 2 H), 5.55 (m, 1 H), 7.22 (s, 5 H). XVII-a: 1.29 (s, 6 H), 1.32 (m, 4 H), 2.57 (d, 2 H), 7.08 (m, 5 H). XVIII-i: 1.05 (t, 3 H), 2.10 (q, 2 H), 3.10 (d, 2 H), 4.7–5.6 (m, 3 H), 7.0–7.5 (m, 10 H). XVIII-a: 0.8–1.5 (m, 5 H), 1.19 (t, 3 H), 2.48 (q, 2 H), 6.8–7.5 (m, 10 H). XIX-i: 0.98 (t, 3 H), 1.33 (s, 3 H), 2.01 (q, 2 H), 3.07 (s, 2 H), 4.35 (m, 1 H), 4.75 (m, 1 H), 6.9–7.6 (m, 10 H). XIX-a: 1.0–1.5 (m, 5 H), 1.10 (t, 3 H), 1.25 (s, 2 H), 2.35 (q, 2 H), 6.8–7.6 (m, 10 H). XX-i: 1.00 (t, 3 H), 1.50 (d, 3 H), 1.95 (q, 2 H), 2.8–3.2 (m, 1 H), 4.70 (m, 2 H), 5.60 (m, 1 H), 7.0–7.5 (m, 10 H). XXI-i: 1.00 (s, 9 H), 3.20 (d, 2 H), 4.93 (m, 2 H), 5.60 (m, 1 H), 6.9–7.6 (m, 10 H). XXI-a: 1.16 (s, 9 H), 1.1–1.5 (m, 3 H), 2.23 (d, 2 H), 6.9–7.4 (m, 10 H).

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all new compounds listed in the table. The nmr spectra are reported in δ units in parts per million downfield from internal TMS.

—To a 100-ml flask equipped with a stirrer were added 10 g (0.04 mol) of diphenylbromomethane and 5 g (0.08 mol) of dimethyl sulfide. The reaction mixture was stirred rapidly for 12 hr. The amorphous solid appeared. The organic layer was completely removed under vacuum. An aqueous solution of 6.6 g (0.06 mol) of sodium fluoroborate was combined with the solid and stirred for 0.5 hr. The reaction mixture was filtered, and the precipitate was washed with ether to yield a gray solid. Recrystallization from acetone–ether afforded 3.4 g (26%) of a pale purple solid: mp 160–161°; ir (KBr) 1630, 1600, 1584, 1491, 1422, and 1130–1010 $cm^{-1}$; nmr (deuterioacetone) 2.09 (s, 6 H), 6.25 (s, 1 H), and 7.2–7.6 ppm (m, 10 H). *Anal.* Calcd for $C_{15}H_{17}SBF_4$: C, 56.99; H, 5.43. Found: C, 56.57; H, 5.91.

**Synthesis of Benzhydryldiethylsulfonium Fluoroborate (XIII).**—To 10 g (0.11 mol) of diethyl sulfide in the flask was added 28 g (0.11 mol) of diphenylbromomethane. To the stirring suspension, 11 g (0.11 mol) of sodium fluoroborate aqueous solution was added. After stirring for 12 hr, the solution was filtered and the precipitate was washed several times with ether. Recrystallization from acetone–ether gave 13 g (29%) of a white solid: mp 115.5–117°; ir (KBr) 1580, 1485, 1445, 1410, 1255, and 1110–1020 $cm^{-1}$; nmr ($CDCl_3$) δ 2.03 (t, 6 H), 3.38 (m, 4 H), 6.11 (s, 1 H), and 7.6–7.9 ppm (m, 10 H). *Anal.* Calcd for $C_{17}H_{21}SBF_4$: C, 58.99; H, 6.44. Found: C, 59.33; H, 6.10.

**Synthesis of Benzhydryldiisopropylsulfonium Perchlorate (XIV).**—The salt was prepared as in the above method using 30 g (0.12 mol) of diphenylbromomethane, 22 g (0.18 mol) of diisopropyl sulfide, and 25 g (0.22 mol) of silver perchlorate. After 20 hr, the yield was 7 g (15%): mp 98–99°; ir (KBr) 1595, 1486, 1442, 1372, 1358, 1232, 1170, 1137, 1108, 1080, and 1022 $cm^{-1}$; nmr ($CDCl_3$) δ 3.11 (d, 12 H), 3.85 (m, 2 H), 5.40 (s, 1 H), and 7.1–7.9 ppm (m, 10 H). *Anal.* Calcd for $C_{19}H_{25}SClO_4$: C, 59.30; H, 6.50. Found: C, 59.18; H, 6.25.

**General Procedure of Photochemical Reactions of Phenyl- and Diphenyldiazomethanes.**—Photolysis of 0.4–2 mmol of phenyl- or diphenyldiazomethanes in 5–20 mmol of a substrate was carried out with a high-pressure mercury lamp in Pyrex vessels without degassing. After the diazo band disappeared from the ir spectrum of the reaction mixture, a known amount of an internal standard was added to the reaction mixture, which was then analyzed by gas chromatography. The structure of the isolated product was determined on the basis of nmr and ir spectra and elemental analysis. The cyclopropane derivatives obtained from the reaction with the allylic system consist of two geometrical isomers, but their configurations were not assigned. Analytical data are reported in Table IV.[26]

**General Procedure of Cupric Sulfate Catalyzed Thermal Reactions.**—Thermal reactions were carried out for 0.4–2 mmol of phenyl- or diphenyldiazomethanes in 5–20 mmol of a substrate in the presence of 20 mg of cupric sulfate. Samples were kept at room temperature or at 70° for the appropriate time. The results obtained are independent of the reaction conditions. The reactions in allylic sulfides were carried out at 110° because of slow reaction.

**General Procedure of Thermal Reactions of Aryldiazomethanes.**—A similar reaction on the same scale was carried out without cupric sulfate. More violent conditions are required to complete the reactions. Samples of phenyldiazomethane were heated at 140° and of diphenyldiazomethane at 70–110°. The products were examined by glpc.

**Reactions of Benzhydryldialkylsulfonium Salts.**—To a stirred suspension of 200 mg (5.1 mmol) of sodium amide in 10 ml of solvent was added, over a period of 10 min, 1.3 mmol of benzhydryldialkylsulfonium salt. The resulting solution was stirred for 20–24 hr. After addition, the reaction mixture was extracted with ether, washed with water several times, and dried over Drierite. The products were analyzed by glpc.

**Photolysis of Phenyldiazomethane in Dimethyl Sulfide.**—Irradiation of a cooled solution of 0.068 g (0.58 mmol) of phenyldiazomethane in 0.6 g (10 mmol) of dimethyl sulfide contained in a Pyrex vessel resulted in the evolution of nitrogen gas. After the infrared spectrum of the reaction mixture showed no diazo band, the reaction products were isolated by glpc using a Carbowax column. The yields shown already were determined by glpc analysis using internal biphenyl.

**Photolysis of Diphenyldiazomethane in Dimethyl Sulfide.**—A solution of 0.516 g (2.66 mmol) of diphenyldiazomethane in 1.65 g (26.6 mmol) of dimethyl sulfide was irradiated. The reaction mixture was analyzed directly by gas chromatography. The results are shown in Table IV.

**Reaction of Phenyldiazomethane in Allylic Sulfides.**—A solution of 0.064 g (0.54 mmol) of phenyldiazomethane in 1.00 g (9.82 mmol) of allyl sulfide was irradiated for 6 hr with a high-pressure mercury lamp. After distillation of solvent, the reaction mixture was purified by gas chromatography. Two major products were collected and characterized as shown in Table IV.

**Reaction of Diphenyldiazomethane in Allyl Sulfide.**—A solution of 76.9 mg of diphenyldiazomethane in 414 mg (4.1 mmol) of allyl ethyl sulfide was cooled with running water and irradiated through Pyrex for 15 hr with a high-pressure mercury lamp. Gas chromatography showed one major product, identified as XVIII-i.

**Thermal Decomposition of Phenyldiazomethane in Allyl Sulfide.**—A solution of 0.06 g of phenyldiazomethane in 1 g (10 mmol) of allyl ethyl sulfide was sealed in a Pyrex tube and heated to 140° for 5 hr. After removal of solvent the residue was chromatographed to yield one major product, XV-a.

**Thermal Decomposition of Diphenyldiazomethane in Allyl Sulfide.**—A solution of 223 mg of diphenyldiazomethane in 722 mg (7.13 mmol) of allyl ethyl sulfide was sealed in Pyrex tubes without degassing and heated at 110° for 1 hr. Analysis of the reaction mixture by gas chromatography showed two major peaks. The new products were tentatively identified by spectral analyses as insertion and addition products of diphenylcarbene to allyl ethyl sulfide.

**Thermal Decomposition of Phenyldiazomethane in Allyl Sulfide in the Presence of Anhydrous Cupric Sulfate.**—A solution of 0.075 g of phenyldiazomethane in 2 g of allyl ethyl sulfide with 20 mg of anhydrous cupric sulfate was sealed in a Pyrex tube and heated at 110° for 30 min. The reaction mixture was analyzed directly by gas chromatography.

**Thermal Decomposition of Diphenyldiazomethane in Allyl Sulfide in the Presence of Anhydrous Cupric Sulfate.**—A solution of 93 mg (0.48 mmol) of diphenyldiazomethane in 0.51 g (4.9

(26) Infrared spectra of these compounds will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-3791. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

mmol) of allyl ethyl sulfide and 20 mg of anhydrous cupric sulfate was sealed in a Pyrex tube and heated at 110° for 3 min. Analysis by infrared spectrum revealed that the reaction was over. Gas chromatography showed one major peak and one minor peak. Spectral analyses indicated that the major peak is the insertion product of the carbene into the carbon–sulfur bond, and the minor peak is the addition product.

**Registry No.**—IB-In, 35906-23-1; IB-r, 35906-24-2; IIA-In, 35906-25-3; IIB-In, 35906-26-4; IIIB-In, 35906-27-5; IIIB-E, 35906-28-6; VIIA-In, 35906-29-7; XII, 35906-30-0; XIII, 35906-31-1; XIII B-r, 35906-32-2; XIV, 35906-33-3; XV-a, 35906-34-4; XV-i, 35905-68-1; XVI-i, 35905-69-2; XVII-a, 35905-70-5; XVII-i, 35905-71-6; XVIII-a, 35905-72-7; XVIII-i, 35905-73-8; XIX-a, 35905-74-9; XIX-i, 35905-75-0; XX-i, 35905-76-1; XXI-a, 35905-77-2; XXI-i, 35905-78-3; phenyldiazomethane, 766-91-6; diphenyldiazomethane, 833-40-9.

# Model Systems Related to Reactivity of Protein Sulfur Functions. I. The Effect of Hydrophobic Bulk on Acid Strengths of Alkyl-Substituted Benzenethiols and on Nucleophilicities of the Benzenethiolate Anions toward *N*-Ethylmaleimide[1]

DOROTHY SEMENOW-GARWOOD

*The Department of Chemistry and Molecular Biology Institute, University of California, Los Angeles, California 90024*

*Received March 29, 1972*

Apparent acid dissociation constants of a series of alkyl-substituted benzenethiols in 95% ethanol are measured by the method of fractional neutralization. Thiol p$K_a$'s correlate well with the p$K_a$'s of the corresponding phenols. Electronic and steric substituent effects are separated (1) by comparison of para- and ortho-substituted isomers and (2) by a Hammett linear-free-energy correlation. The substantially lower acidity of 2-*tert*-butylbenzenethiol compared to the other benzenethiols studied is attributed to steric inhibition of solvation of the thiolate anion rather than to direct steric interactions between the *tert*-butyl group and the adjacent sulfur. The rates of addition of the alkyl-substituted benzenethiols to *N*-ethylmaleimide in 95% ethanol at 25° are reported. The rate of attack of ortho-alkyl-substituted benzenethiolate anion upon the olefinic double bond of *N*-ethylmaleimide is sensitive to the size or bulk of the alkyl group. Two effects are identified: (1) inhibition of solvation of the thiolate anion, which increases its nucleophilicity (rate accelerating), and (2) steric interference between the thiolate nucleophile and the olefin transition state (rate retarding). The first known example of net steric acceleration in a nucleophilic addition to an activated double bond is reported for *o-tert*-butylbenzenethiolate which is found to be an order of magnitude more reactive than the other alkylbenzenethiols studied. The implications of the results as regards hydrophobic bulk effects in enzymatic reactions involving mercaptide functions are discussed.

The specific modification of only the most reactive protein sulfhydryl groups with activated double bond reagents such as *N*-ethylmaleimide (NEM) and acrylonitrile has encouraged their use as probes of SH environment and catalytic involvement.[2] Although it is generally supposed that such factors as location in the three-dimensional protein structure, microscopic environment or neighboring group effect, and interaction with other functional groups determine the rates of SH addition across the double bond of NEM,[3] few studies to evaluate the relative importance of the various factors are available.[4] Furthermore, SH group acid strengths affect the differential nucleophilic reactivities of protein sulfhydryl groups with SH modification reagents. While thiol acid strength as a function of electrical substituent effects has been the focus of previous investigations,[5,6] the effects of hydrophobic bulk on thiol dissociation has remained relatively unexplored. The findings from several protein studies, which indicate that SH groups frequently lie in interior hydrophobic locations,[7,8] suggested that investigation of thiol acid strength and of thiolate nucleophilicity in reaction with NEM as a function of nearby hydrophobic bulk should contribute to the understanding of protein SH group reactivities. Thus, we now report p$K_a$ and kinetic studies with a series of alkyl-substituted benzenethiols selected to assess steric effects on acidity and rates of addition to NEM.

## Results

The series of thiols investigated included benzenethiol and its alkyl substituted derivatives: 4-methyl; 3-methyl; 2-methyl; 2,6-dimethyl; 4-*tert*-butyl; and 2-*tert*-butyl.

The solubility properties of the aromatic thiols dictated that the p$K_a$ measurements be performed in 95% ethanol solvent, a medium which approximates more closely than does water the probable hydrophobic environment of many protein SH groups. The absolute pH values obtained in such a medium by the potentiometric methods are not subject to simple

(1) This investigation was supported in part by Grant No. GM 11094 from the Institute of General Medical Sciences, U. S. Public Health Service, and by Contract AT(04-3)-34, Project 102, of the U. S. Atomic Energy Commission; P. D. Boyer, principal investigator.

(2) L. Cohen in "Annual Review of Biochemistry," Vol. 37, P. D. Boyer, Ed., Annual Reviews, Inc., Palo Alto, Calif., 1968, p 695.

(3) J. F. Riordan and B. L. Vallee in "Methods in Enzymology," Vol. 11, C. H. W. Hirs, Ed., Academic Press, New York, N. Y., 1967, p 451.

(4) Quantitative estimates of the influence of some polar and steric reaction parameters on the rates of addition of cysteine derivatives to acrylonitrile in water have been reported: M. Friedman, J. F. Cavins, and J. S. Wall, *J. Amer. Chem. Soc.*, **87**, 3671 (1965).

(5) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch, *ibid.*, **82**, 4899 (1960).

(6) J. P. Danehy and C. J. Noel, *ibid.*, **82**, 2511 (1960).

(7) R. Cecil, "The Protons," Vol. 1, 2nd ed, H. Neurath, Ed., Academic Press, New York, N. Y., 1963, p 380.

(8) For example, in human hemoglobin the cysteinyl residue at G11 of the $\alpha$ subunit is inaccessibly located in the interior.[9] Cysteine G14 of the $\beta$ chain is in the hydrophobic contact area between the $\alpha_1$ and $\beta_1$ subunits, and only the sulfhydryl group at F9 protrudes into the medium.[9]

(9) M. F. Perutz, H. Muirhead, J. M. Cox, and L. C. G. Goaman, *Nature (London)*, **217**, 131 (1968); M. F. Perutz, *J. Mol. Biol.*, **13**, 646 (1965).

TABLE I

RELATIVE ACID DISSOCIATION CONSTANTS OF ARENETHIOLS (ARSH) IN 95% ETHANOL AT 25.0 ± 0.2°

| ArSH[a] | Number of runs | $pK_a$, apparent av ± std dev | $K_{a,PhSH}/K_{a,ArSH}$ |
|---|---|---|---|
| PhSH | 8 | 9.58 ± 0.06 | 1.0 |
| 4-MePhSH | 4 | 9.95 ± 0.01 | 2.4 |
| 3-MePhSH | 4 | 9.80 ± 0.01 | 1.6 |
| 2-MePhSH | 5 | 10.22 ± 0.03 | 4.5 |
| 2,6-DiMePhSH | 6 | 10.77 ± 0.02 | 15.6 |
| 4-*tert*-BuPhSH | 4 | 9.90 ± 0.02 | 2.1 |
| 2-*tert*-BuPhSH | 8 | 11.64 ± 0.13 | 115 |

[a] Registry numbers are, respectively, 108-98-5, 106-45-6, 108-40-7, 137-06-4, 118-72-9, 2396-68-1, 19728-41-7.

interpretation owing to the indeterminate potential at the junction: solution X (95% alcohol)/KCl bridge (aqueous). However, Bates and coworkers[10] found that the liquid-junction potential is *constant* for different buffers in alcoholic solvents of *fixed* composition, so that the contribution of junction potential to measured pH is not reflected in the *relative* $pK_a$ values.

The apparent acid dissociation constant data of the thiols as determined by the neutralization method are summarized in Table I. There is good agreement between the 30 and 50% neutralization values.

The spectrophotometric $pK_a$ for 2-methylbenzenethiol is 10.44. The 0.2 discrepancy between this value and that obtained by the neutralization method may result in whole or in part from neglect of hydrolysis correction in the latter value.

Correction of the measured pH values for liquid-junction potential and medium salt effects according to the method of Bates, *et al.*,[10] would raise all of the $pK_a$ values about 0.7 unit. As has been observed previously for carboxylic acids[11] and thiols,[12] replacement of an aqueous environment by one of higher hydrocarbon content (lower dielectric constant) such as 95% ethanol markedly weakens the acid strength.

Spectrophotometric determinations of the kinetics of the reaction of each of the alkyl-substituted benzenethiols with NEM were performed in 95% ethanol at a series of buffered pH's. Control experiments as described in the Experimental Section established the reliability of the kinetic assays, the assigned stoichiometry, the absence of side reactions, and the exclusive formation of the addition products, α-arylthio-*N*-ethylsuccinimides.

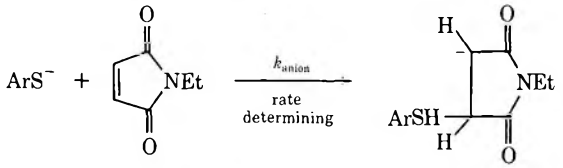
The kinetic data are summarized in Table II. The variation of $k_{obsd}$ and constancy of $k_{anion}$ over the range of pH investigated indicates that the thiolate anion is the sole reactive species in the rate-determining step which is consistent with the mechanism of eq 1–3. If the neutral thiol molecule were to show significant nucleophilic reactivity in the addition to NEM, the observed rate constant would be given by eq 4 and a plot of $k_{obsd}(H^+)$ *vs.* $(H^+)$ would give a significant positive slope equal to $k_{thiol}$. Such a plot of the data reveals a zero slope within the limits of experimental error. Thus, $k_{thiol}$ must be less than the experimental error of the data ($\leq 7\%$ of $k_{anion}$).

(10) R. G. Bates, M. Paabo, and R. A. Robinson, *J. Phys. Chem.*, **67**, 1833 (1963).

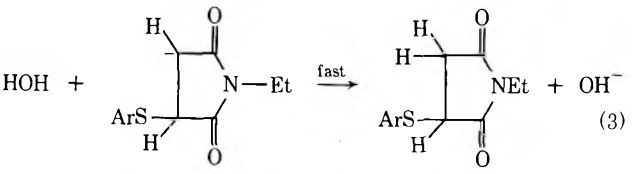
(11) E. Grunwald and B. J. Berkowitz, *J. Amer. Chem. Soc.*, **73**, 4939 (1951).

(12) B. Dmuchovsky, F. B. Zienty, and W. A. Vredenburgh, *J. Org. Chem.*, **31**, 865 (1966).

$$ArSH + OH^- \underset{}{\overset{K_a}{\rightleftharpoons}} ArS^- + HOH \quad (1)$$



(2)



(3)

$$k_{obsd} = \frac{k_{anion}K_a}{(H^+)} + k_{thiol} \quad (4)$$

For all runs the fit of the data to an integrated second-order line gave a standard deviation of points from the line of ~1% or less of the $k$ values. The standard deviations for the $k_{obsd}$ values obtained at a given pH are ≤7% of the average values, and for the $k_{anion}$ values for a given thiol over the entire range of 1.5 pH units are 2.2–7.2% of the average $k_{anion}$ values.

The small (10%) rate increase observed with threefold increase in buffer concentration signifies that general acid catalysis by acetic acid and ionic salt effects are relatively unimportant.

The $k_{anion}$ values for all $ArS^-$ are comparable (within a factor of 2) except for 2-*tert*-butylbenzenethiolate anion for which the $k_{anion}$ value is 17 times that for the unsubstituted benzenethiolate anion.

## Discussion

**Acidity.**—For most chemical reactions of ortho-substituted reactants, the ortho effects observed are not primarily due to steric effects[13] except for groups of considerable bulk such as *tert*-butyl. Thus, it is predicted and borne out by the present acidity measurements reported in Table I that the *tert*-butyl compound is a considerably weaker acid than the other benzenethiols which are unsubstituted or substituted with the smaller methyl group in the ortho position.

The acid strengths of meta- and para-substituted benzenethiols and phenols are known to parallel each other.[14,15] We have found that this correlation continues to hold when extended to ortho substitution of a bulky group such as *tert*-butyl.[16] *o*-*tert*-Butylbenzenethiol is 55 times a weaker acid than is the para isomer as measured in 95% ethanol in the present work; the factor is 65 for the corresponding phenols where the

(13) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615, 619, 624, 6649 (1969).

(14) G. Schwarzenbach and E. Rudin, *Helv. Chim. Acta*, **22**, 360 (1939).

(15) A linear least-squares regression was applied to the $pK_a$ data of Schwarzenbach and Rudin[12] for 18 pairs of phenols and benzenethiols. A good straight line was obtained with slope $d(pK_a^{ArOH})/d(pK_a^{ArSH}) = 1.004$, standard deviation 0.016, and correlation coefficient 0.9978.

(16) A linear least-squares regression was employed to correlate the acidities of the benzenethiols of Table I and the corresponding phenols of Table III.[17] The straight line obtained had a slope of 0.983, a standard deviation of 0.033, and a correlation coefficient of 0.997. When the 2-*tert*-butyl derivatives were excluded from the correlation, the slope was 0.889, standard deviation 0.041, and correlation coefficient 0.996.

(17) (a) C. H. Rochester, *J. Chem. Soc.*, 676, 4603 (1965). (b) C. H. Rochester, *J. Chem. Soc. B*, 121 (1966). (c) C. H. Rochester, *Trans. Faraday Soc.*, **62**, 355 (1966). (d) C. H. Rochester and B. Rossall, *J. Chem. Soc. B*, 743 (1967). (e) C. H. Rochester, *Trans. Faraday Soc.*, **65**, 1004 (1969).

acid strengths shown in Table II were measured spectrophotometrically at 25° in methanol (Table III).[17,18]

The comparison between ortho-alkylated benzenethiols and the corresponding phenols illuminates the cause of the acid weakening effect of an *o-tert*-butyl group. Although sulfur is a much larger and more polarizable atom than oxygen, substitution of a *tert*-butyl group in the ortho position has similar effects on the acid strengths of both benzenethiol and phenol. The acid weakening effect in the thiol is evidently not due to severe steric repulsion between the sulfur and adjacent alkyl group since a similar effect is observed for the smaller oxygen atom. This conclusion is further supported by an examination of space-filling CPK molecular models which provide reasonable estimates of van der Waals radii. The models show that the sulfur and the *tert*-butyl groups, although in close proximity, can be accommodated in adjacent positions on the benzene ring without distortion. Any repulsion which may exist in the actual molecule can be relieved without loss of sulfur-ring $\pi$ resonance by a bending of the sulfur–carbon bond *in the plane of the ring* away from the *tert*-butyl group. It is concluded that steric inhibition of resonance in the *o-tert*-butylbenzenethiolate anion does *not* explain the decrease in acidity of the corresponding thiol.

Rather, the large diminution of acid strength for *o-tert*-butylbenzenethiol is attributed to steric inhibition of solvation[21,22] by the adjacent hydrocarbon bulk in the ortho anion. The substitution of a large alkyl group of low effective dielectric constant and of poor hydrogen-bonding ability displaces solvent of higher dielectric constant and good hydrogen-bonding capacity. The exclusion of polar solvent molecules by the alkyl group from a region near a charged group, such as the thiolate anion, increases the free energy of the anion by reduction of solvation stabilization of the charge.

Steric inhibition of solvation of the unionized benzenethiols (*i.e.*, decreased hydrogen bonding of the –SH function with solvent) increases their acidities by raising the ground-state energies. This effect on acidity is in the opposite direction to the corresponding effect on the anions. However, solvation of the full negative charge of the anion is far more important energetically than solvation of the neutral species. Therefore, to a first approximation the effects of steric inhibition of solvation on the neutral thiol molecules may be ignored.

An estimate of the steric effects of *o*-methyl and *o-tert*-butyl substituents can be obtained by two methods. The first and simpler method is a comparison of the acidities of the *o*- and *p*-alkylbenzenethiols. Since the electron-donating capacities of the para alkyl groups are slightly greater than the corresponding ortho groups,[23] the amount of acid weakening observed for the para isomers may be considered as the maximum owing to destabilization of the anion by the *electronic* effects of a single ortho alkyl substituent. Further decrease in acidities of the ortho isomers beyond that attributable to electron release by the ortho alkyl groups (see Table I) is only a factor of 2 for the *o*-methyl compound, but reaches the considerable magnitude of 55, equivalent to a free-energy increment of 2.4 kcal/mol, for the *tert*-butyl species.

The second approach to assessment of steric inhibition to solvation for ortho substituents involves a Hammett $\sigma^-$ plot[23,26] of the p$K_a$'s of substituted benzenethiols as shown in Figure 1.[27]

The deviations of ortho-substituted benzenethiols from the line defined by the para and meta derivatives provides a measure of the importance of steric inhibition of solvation. The correlation for 14 unhindered aromatic thiols[28] has a slope of $\rho = 2.422 \pm 0.140$, correlation coefficient 0.981.[29] The deviations in p$K_a$ units are 0.42 for 2-methyl, 0.68 for 2,6-dimethyl, and 1.98 for 2-*tert*-butyl substituents. These deviations correspond to free energies for the ortho "steric inhibition of solvation" effect of 0.6 kcal/mol for a single methyl, 0.9 kcal/mol for two methyls, and 2.7 kcal/mol for a *tert*-butyl group. The latter value agrees well with the simple estimate made above (2.4 kcal/mol) for the contribution of the effect of steric inhibition of solvation to the energy of the *o-tert*-butylbenzenethiolate anion.

Thus, the steric inhibition of solvation effect is negligible or minor for *o*-methyl substituents but attains a significant magnitude for a single *o-tert*-butyl group in this system. The large destabilization observed for this bulky group probably reflects the loss of one or more hydrogen bonds between the solvent and the thiolate anion.

**Nucleophilicity.**—The addition of ortho-substituted benzenethiolate anions to NEM may be subject to two opposing steric effects. The steric inhibition of solvation effect involves interference by the adjacent alkyl hydrocarbon bulk with protic solvent solvation of the anionic sulfur. Therefore, operation of this effect on the thiolate addition to NEM raises the energy of the thiolate ground state, lowers the desolvation component of the activation energy, and increases the rate constant, $k_{anion}$. A second effect decreases the rate of

(18) The ordering of substituent effects on acidities of a series of related phenols for a transfer from a given protic solvent to a related protic solvent should remain invariant.[17d,19,20] Thus, the fact that benzenethiol and phenol dissociation constants used in the correlation treatment were measured in different solvents (95% ethanol and methanol, respectively) does not invalidate the conclusion that the effect of *o-tert*-butyl substitution produces similar effects upon benzenethiol and phenol ionizations.

(19) L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963).

(20) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *ibid.*, **88**, 1911 (1966).

(21) P. D. Bartlett, *J. Chem. Educ.*, **30**, 22 (1953); P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, **76**, 2349 (1954).

(22) G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).

(23) Hammett sigma constants ($\sigma^-$) for para and meta substituents are tabulated by Ritchie and Sager;[24] the para values are −0.17 for methyl and −0.20 for *tert*-butyl. The ortho $\sigma^-$ constants, apparently free from steric effects, are −0.13 for methyl and −0.08 for *tert*-butyl.[25]

(24) C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitsieser, Jr., and R. W. Taft, Ed., Interscience, New York, N. Y., 1964, p 323.

(25) M. T. Tribble and J. G. Traynham, *J. Amer. Chem. Soc.*, **91**, 379 (1969).

(26) The $\sigma^-$ constant for 2,6-dimethyl substitution was assumed to be twice the value for *o*-methyl, *i.e.*, −0.26.

(27) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Chapter 13, Wiley, New York, N. Y., 1956.

(28) The p$K_a$ values reported by Schwarzenbach and Rudin[14] in 95% ethanol at 20–22° were adjusted to the p$K$ scale for values in Table I by addition of 0.25 p$K$ unit. The value for 4-*tert*-butyl from this work (Table I) was included in the plot.

(29) Jaffé[30] obtained $\rho = 2.847 \pm 0.150$ for 12 benzenethiol p$K_a$'s (Schwarzenbach and Rudin[14]) correlated with Hammett's original unadjusted $\sigma$ (not $\sigma^-$). Bordwell and Andersen[31] obtained $\rho = 2.578$ for 12 arylthiol p$K_a$'s (in 48% ethanol at 25°) when correlated with $\sigma$.

(30) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(31) F. G. Bordwell and H. M. Andersen, *J. Amer. Chem. Soc.*, **75**, 6019 (1953).

TABLE II
SECOND-ORDER RATE CONSTANTS FOR REACTIONS OF *N*-ETHYLMALEIMIDE AND ARYLTHIOLS IN 95% ETHANOL AT 25.0 ± 0.2°

| ArSH | Run no. | Initial concn × 10 (ArSH)$_0$ | Initial concn × 10 (NEM)$_0$ | pH[a-c] | % reaction completion on which $k$ is based | $k_{obsd}$[d,e] ($M^{-1}$ sec$^{-1}$) | $k_{anion}$[d,f] × 10$^{-4}$ ($M^{-1}$ sec$^{-1}$) ± std dev |
|---|---|---|---|---|---|---|---|
| PhSH | 1 | 19.64 | 5.56 | 5.43 | 33 | 1.20 | 1.67 |
| | 2 | 9.82 | 11.14 | 5.43 | 18 | 1.29 | 1.81 |
| | 3 | 9.78 | 10.63 | 6.24 | 60 | 8.59 | 1.86 |
| | 4 | 9.81 | 10.47 | 6.91 | 87 | 43.0 | 2.00 |
| | 5 | 9.81 | 10.47 | 6.91 | 70 | 45.3 | 2.10 |
| | 6 | 5.89 | 12.56 | 6.91 | 76 | 41.8 | 1.93 |
| | | | | | | Av | 1.90 ± 0.14 |
| 4-MePhSH | 7 | 8.56 | 9.10 | 5.43 | 33 | 1.27 | 4.22 |
| | 8 | 43.60 | 8.11 | 6.24 | 95 | 7.80 | 4.01 |
| | 9 | 11.11 | 8.47 | 6.24 | 50 | 7.81 | 4.01 |
| | 10 | 2.29 | 12.49 | 6.24 | 79 | 7.79 | 4.01 |
| | 11 | 4.45 | 7.37 | 6.91 | 60 | 38.1 | 4.19 |
| | 12 | 2.67 | 8.85 | 6.91 | 68 | 37.7 | 4.13 |
| | | | | | | Av | 4.10 ± 0.09 |
| | 13 | 18.28 | 11.71 | 6.29[g] | 64 | 9.64 | 4.41 |
| | 14 | 9.14 | 11.71 | 6.29[g] | 59 | 10.1 | 4.64 |
| | | | | | | Av | 4.53 ± 0.12 |
| 4-*tert*-BuPhSH | 17 | 17.30 | 5.50 | 5.43 | 44 | 1.15 | 3.42 |
| | 18 | 15.00 | 5.05 | 6.24 | 68 | 8.60 | 3.96 |
| | 19 | 7.50 | 10.10 | 6.24 | 47 | 8.29 | 3.82 |
| | 20 | 7.13 | 10.43 | 6.91 | 67 | 39.3 | 3.87 |
| | 21 | 4.23 | 12.51 | 6.91 | 83 | 41.6 | 4.10 |
| | | | | | | Av | 3.83 ± 0.23 |
| 3-MePhSH | 22 | 21.09 | 5.57 | 5.43 | 74 | 1.20 | 2.81 |
| | 23 | 10.54 | 11.14 | 5.43 | 13 | 1.28 | 2.99 |
| | 24 | 18.89 | 5.16 | 6.24 | 74 | 7.29 | 2.63 |
| | 25 | 9.44 | 10.33 | 6.24 | 32 | 8.02 | 2.90 |
| | 26 | 5.37 | 12.52 | 6.91 | 73 | 37.3 | 2.88 |
| | | | | | | Av | 2.84 ± 0.12 |
| 2-MePhSH | 27 | 71.62 | 10.81 | 5.43 | 53 | 0.452 | 2.81 |
| | 28 | 67.88 | 10.66 | 5.43 | 24 | 0.441 | 2.75 |
| | 29 | 33.94 | 10.66 | 5.43 | 46 | 0.449 | 2.79 |
| | 30 | 33.21 | 10.44 | 6.24 | 66 | 3.20 | 3.07 |
| | 31 | 33.14 | 10.57 | 6.24 | 82 | 3.20 | 3.07 |
| | 32 | 16.57 | 10.57 | 6.24 | 55 | 3.04 | 2.91 |
| | 33 | 21.60 | 5.00 | 6.91 | 80 | 15.2 | 3.12 |
| | 34 | 10.81 | 10.00 | 6.91 | 64 | 15.2 | 3.12 |
| | | | | | | Av | 2.96 ± 0.15 |
| 2,6-DiMePhSH | 37 | 79.76 | 11.27 | 5.43 | 36 | 0.141 | 3.09 |
| | 38 | 39.88 | 11.27 | 5.43 | 28 | 0.139 | 3.04 |
| | 39 | 74.63 | 11.43 | 6.24 | 76 | 0.809 | 2.74 |
| | 40 | 37.31 | 11.43 | 6.24 | 54 | 0.816 | 2.75 |
| | 41 | 45.38 | 11.84 | 6.91 | 78 | 4.11 | 2.97 |
| | 42 | 45.38 | 11.84 | 6.91 | 85 | 4.23 | 3.02 |
| | 43 | 22.69 | 11.84 | 6.91 | 63 | 4.23 | 3.07 |
| | | | | | | Av | 2.96 ± 0.14 |
| 2-*tert*-BuPhSH | 46 | 13.25 | 13.25 | 6.91 | 60 | 6.26 | 33.6 |
| | 47 | 13.25 | 13.25 | 6.91 | 48 | 5.88 | 31.6 |
| | 48 | 13.25 | 13.25 | 6.91 | 35 | 6.44 | 34.5 |
| | 49 | 10.00 | 10.00 | 6.91 | 80 | 6.43 | 34.5 |
| | 50 | 25.00 | 10.00 | 6.91 | 72 | 6.19 | 33.2 |
| | 51 | 30.00 | 7.00 | 6.91 | 61 | 5.95 | 31.9 |
| | | | | | | Av | 33.2 ± 1.14 |

[a] All pH measurements are uncorrected for junction potential (95% ethanol–water). [b] pH values are averages of five determinations; standard deviations are 0.02–0.03. [c] All buffers are 0.01 $M$ in total acetic acid plus potassium acetate concentration unless otherwise specified. [d] Defined by equation d(product)/d$t$ = $k_{obsd}$(NEM)(ArSH) = $k_{anion}$(NEM)(ArS$^-$). [e] All $k_{obsd}$ values are based on 5–13 kinetic points and for most runs on ≥7 points. [f] The p$K_a$ values in 95% ethanol used in calculation of $k_{anion}$ are reported in Table I. [g] Total concentration of acetic acid plus potassium acetate is 0.03 $M$.

anion attack on the double bond (rate constant $k_{anion}$) owing to steric crowding in the transition state. Thus, for the NEM reactions, the influences of the steric inhibition of solvation effect on the ground state and of steric crowding in the transition state are opposed.

Since in the transition state for the rate-determining step of eq 2, the anionic charge is dispersed over the conjugated NEM system as well as the benzenethiol system, steric hindrance to solvation of the transition state is relatively unimportant compared with that of the ground-state thiolate anion.

Whereas the predominance of the decelerating crowd-

ing effect is usually observed, as in the case of the decreased rate of tertiary alkyl thiolate addition to acrylonitrile relative to primary alkyl thiolate,[4] the remarkable feature of the current results (Table II) is that, for the *o-tert*-butylbenzenethiolate anion, the accelerating effect of steric inhibition of solvation prevails to render it 8.7 times as reactive as the para isomer. (The electronic effects would slightly favor the para thiolate.[32]) We may conclude that, although solvent is to some appreciable degree excluded from the vicinity of the anionic sulfur in the hindered ortho species as indicated by its increased basicity, the approach of the thiolate center to the olefinic carbon in NEM as required in the transition state is not prevented to the same degree. Presumably, the partially formed sulfur–carbon bond in the transition state is sufficiently long to accommodate the adjacent steric bulk.

The following estimation of the relative magnitudes of accelerating effect of steric inhibition of solvation and decelerating steric crowding effects employs the Brønsted correlation between the logarithms of the rate constants and the logarithms of the acid strengths ($pK_a$'s). To the extent that the factors which determine the rates and acidities are identical, a linear relationship between the rate and acidity data will be obtained.

A Brønsted treatment by the present author of the $pK_a$ data of Schwarzenbach and Rudin[14] and the kinetic data of Krishnamurthy and Miller[33] for the addition of seven thiols to the triple bond of ethyl phenylpropiolate gave a correlation coefficient of 0.984. Although no quantitative treatments of the data were performed, parallels have also been observed between thiol $pK_a$'s and thiolate nucleophilicities for additions of arylthiolate anions to the double bond of maleic anhydride[12] and reactions of mercaptide ions with ethylene oxide.[6]

Divergence of a given thiolate from the linear Brønsted plot reflects a noncorrespondence in the factors determining the rate and acidity values. A Brønsted plot of the data from the present study in Figure 2 shows a linear relationship for the four isomers which lack ortho substituents; the ortho-substituted species deviate from the line so defined.[34] The steric inhibition of solvation effect influences both the $k_{anion}$ and $pK_a$ values in a comparable manner; so it does not contribute to the deviations. The only positive influence on the rate data which is *not* reflected in the acidity constants is steric crowding in the transition state. This is reasonable since formation of a partial bond between a thiolate sulfur and a carbon in the transition state for addition to NEM involves juxtaposition of two multiatomic molecules wherein steric repulsions can become important. By contrast, the proton is very small; so its capture by thiolate anion in the acid–base equilibrium would not be expected to be subject to strong steric hindrance. The increment in the free energy of activation due to steric crowding is estimated for the ortho-substituted thiolates from their deviations from the linear plot as 0.5 kcal/mol for a single methyl, 1.2 kcal/mol for two methyls, and 0.9 kcal/mol for a *tert*-butyl; the corresponding rate deceleration factors are 2.4, 7.9, and 4.5, respectively.

Correction for the steric crowding rate deceleration effect for the *o-tert*-butylbenzenethiolate addition to NEM, which shows the largest observed *net rate enhancement*, gives a total acceleration from steric inhibition of solvation by a factor of at least 39 for the ortho

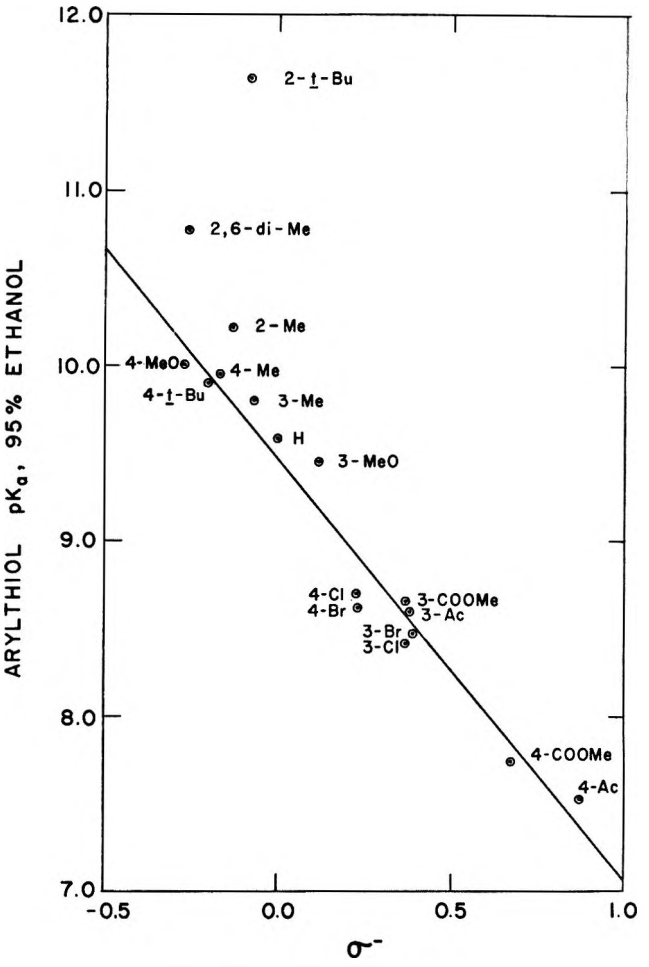



Figure 1.—Hammett $\sigma^-$ correlation of benzenethiol acidities in 95% ethanol.

TABLE III
ACID DISSCCIATION CONSTANTS OF PHENOLS[a] (ArOH) IN METHANOL AT 25°

| ArOH | $pK_a$ |
|---|---|
| PhOH | 14.46 |
| 4-MePhOH | 14.76 |
| 3-MePhOH | 14.59 |
| 2-MePhOH | 15.01 |
| 2,6-DiMePhOH | 15.48 |
| 4-*tert*-BuPhOH | 14.65 |
| 2-*tert*-BuPhOH | 16.46 |

[a] Reference 17.

(32) The reactive anionic center is slightly more negative for the para isomer; $\sigma^-$ constants, apparently free from steric effects are, for *o-tert*-butyl, −0.08 and, for *p-tert*-butyl, −0.20.[25]

(33) G. S. Krishnamurthy and S. I. Miller, *J. Amer. Chem. Soc.*, **83**, 3961 (1961).

(34) As a consequence of the adverse physiological reactions experienced by all experimenters exposed to the thiols for continuous periods, the sequence of thiols was not extended beyond those reported in Table II. Thus, the Brønsted straight line of Figure 2 is based only on the data for the four thiols which lack ortho substituents and cover a limited range of about 0.4 $pK$ units. The line obtained has a slope (Brønsted $\beta$) of 0.921, standard deviation of 0.070, and correlation coefficient of 0.994. An unlikely error of as much as 30% in $\beta$ does not change the qualitative conclusion that the steric inhibition of solvation effect dominates over steric repulsions between reactants.

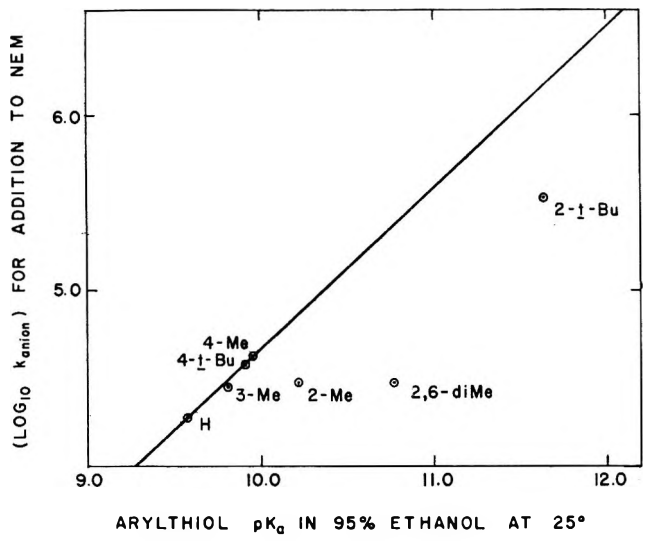



Figure 2.—A Brønsted plot of the arylthiol p$K_a$ data and the arylthiolate-NEM reactivity values at 25° in 95% ethanol

over the para isomer,[35] a ratio which approaches the value of 55 observed for $K_{a,p\text{-}tert\text{-}butyl}/K_{a,o\text{-}tert\text{-}butyl}$.

The above interpretation of our results has implications for those enzymic reactions in which conversion of a thiol function to a thiolate anion is prerequisite to nucleophilic attack on carbon. Differences in the hydrophobic environment of several thiol groups in a single protein or for a single thiol group in two distinct protein conformations can probably produce variations in p$K_a$ of 1–2 units or more. This finding emphasizes that, for cysteinyl residues imbedded in hydrophobic locales, the strategic proximity within the protein of basic functions capable of accepting a proton from the SH function would seem to be essential for the ionization prerequisite to nucleophilic reactivity.

While the present investigation specifically covers only thiolate nucleophilic attack on a trigonal olefinic carbon, it seems reasonable that the conclusions might be extended at least to thiolate reactions at trigonal carbonyl carbons such as in the formation of thiol esters. The thiol function may be situated on the enzyme itself or on a cofactor or substrate. The functionality susceptible to thiolate nucleophilic attack may be located on an external reagent such as NEM, acrylonitrile, or maleic anhydride; on an enzyme molecule which may or may not also harbor the reactive thiol; or on an enzymatic cofactor or substrate.

Our results indicate that optimum reactivity for such systems is attained by the strategic positioning of the thiol: (1) for accessibility to a basic function for proton removal; and (2) in a hydrophobic locale which excluded polar protic solvent molecules and thereby fosters a rate enhancement due to steric inhibition of solvation of the reactant thiolate, but which is sufficiently open and flexible or functionally configured to admit and allow reaction with substrates. Binding of substrate or cofactor or ionization of the thiol group may cause conformational changes which create these conditions for maximum thiol reactivity.

In conclusion, the steric inhibition of solvation effect may be one important contributor to the means by which enzymes under mild conditions in aqueous media so rapidly catalyze reactions which otherwise require organic solvents, elevated temperatures, strong acidic or basic catalysts, or a combination of these.

(35) This estimate does not include correction for electronic effects which favor the para isomer slightly; so the actual magnitude of the steric inhibition of solution effect is probably somewhat larger.

## Experimental Section

**Solvent.**—Ethanol (95%) was purified by distillation of the azeotrope through a 1.5 ft × 1 in. column packed with glass helices, collected under nitrogen, and degassed by bubbling nitrogen through a fritted disk into the solvent for at least 4 hr. The solvent was stored under argon.

**Arylthiols.**—The following thiols were obtained commercially: benzenethiol; 4-, 3-, and 2-methylbenzenethiol; and 4-*tert*-butylbenzenethiol. 2-*tert*-Butylbenzenethiol and 2,6-dimethylenzenethiol were synthesized from the corresponding phenols *via* thermal rearrangements of the *O*-aryl *N*,*N*-dimethylthiocarbamate derivatives as described by Newman and Karnes[36] with the following modifications. Purification of the *O*-aryl dimethylthiocarbamates by chromatography on silica gel with elution by methylene chloride gave better yields (83%) of the *S*-aryl dimethylthiocarbamates obtained from pyrolyses of the *O*-aryl isomers. Whereas Newman and Karnes[36] reported a downfield shift in the nmr bands for the *N*-methyl groups in proceeding from the *O*-aryl dimethylthiocarbamates (doublets at $\tau$ 7.1–7.3) to the corresponding *S*-aryl compounds (singlets at $\tau$ 7.0–7.1), we observed a shift in the opposite direction for our compounds[37] from doublets at $\tau$ 6.6–6.7 for the *O*-aryl compounds to singlets at $\tau$ 7.0–7.3 for the *S*-aryl isomers as measured at 60 MHz on a Varian A-60D nmr spectrophotometer.

Preparations of the arenethiols from the *S*-aryl dimethylthiocarbamates were accomplished by refluxing with ethanolic KOH. The 2,6-dimethyl compound required 48 hr for completion of the hydrolysis. The products were worked up by *in vacuo* removal of solvent, addition of water followed by acidification with 6 *N* $H_2SO_4$, addition of zinc dust, and steam distillation under nitrogen. The thiols were extracted from the steam distillate with ether, the ether extract was dried over $MgSO_4$, the ether was removed by distillation, and the thiols were purified by vapor phase chromatography.

**Purification of Arenethiols.**—Solid 4-methylbenzenethiol was purified by recrystallization from ethyl alcohol to give a white crystalline solid, mp 44.0–44.8°.

The benzenethiols other than the 4-methyl compound are liquids and were purified by vapor phase chromatography on an Aerograph A90P preparative instrument using a 20 ft × $^3/_8$ in. cyanosilicon-coated (17%) firebrick (60/80 mesh) or Chromosorb W column at column temperatures in the 180–225° range. Helium carrier gas was used, and the collected thiols were stored under argon. All thiols (commercial and synthesized) gave 10–20 impurity peaks in addition to the major band. The thiol fractions collected were shown by recycling to consist of a single peak. Structures and purities were confirmed by nmr spectra and carbon–hydrogen microanalyses. *Anal.* Calcd for benzenethiol, $C_6H_6S$: C, 65.40; H, 5.49. Found: C, 65.54; H, 5.49. Calcd for methylbenzenethiols, $C_7H_8S$: C, 67.67; H, 6.50. Found for 2-methylbenzenethiol: C, 67.75; H, 6.57. Found for 3-methylbenzenethiol: C, 67.51; H, 6.62. Found for 4-methylbenzenethiol: C, 67.90; H, 6.58. Calcd for 2,6-dimethylbenzenethiol, $C_8H_{10}S$: C, 69.54; H, 7.30. Found: C, 69.69; H, 7.32. Calcd for *tert*-Butylbenzenethiols, $C_{10}H_{14}S$: C, 72.23; H, 8.49. Found for 2-*tert*-butylbenzenethiol: C, 72.36; H, 8.55. Found for 4-*tert*-butylbenzenethiol: C, 72.26; H, 8.44.

**Measurement of Acid Dissociation Constants.**—All vessels used for thiols were flushed with *nitrogen* or argon to minimize air oxidation of thiols. All pH measurements were made under argon at 25.0 ± 0.2° using a Copenhagen Radiometer pH meter no. 26 with glass–calomel (aqueous) electrode pair standardized with two aqueous buffers. The base employed for neutralization of thiols was 0.1 *N* KOH in 95% ethanol. Apparent $K_a$ values were determined in 95% ethanol by the method of fractional (30 or 50%) neutralization. The equivalents of thiolate anion

(36) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

(37) Although the 2-*tert*-butylaryl and 2,6-dimethylaryl compounds for which nmr spectra were measured in this work are not identical with any in the Newman and Karnes[36] series, the latter series did include the 2,3,5,6-tetramethyl, 2,6-di-*tert*-butyl-4-methyl, and 4-*tert*-butyl derivatives.

($ArS^-$) formed were assumed equal to the equivalents of $OH^-$ base added; no corrections were made for hydrolytic reversal of the neutralization. The concentration of $ArS^-$ at 50% neutralization was kept constant at 0.1 *M* for all runs to eliminate errors due to differences in ionic strength.

Spectrophotometric determination of the $pK_a$ for 2-methylbenzenethiol was performed as a check on the fractional neutralization method. Since the spectral method gives $(ArS^-)/(ArSH)$ directly, no corrections due to hydrolysis are required. This advantage of the spectral method is offset by the fact that the extinction coefficient ($1.9 \times 10^4$) for the thiolate anion at 2.68.5 nm (where the difference in extinction coefficients between anion and molecule is maximum) is so high that even with the shortest path cells available (0.1 mm), the solution for OD measurement must be <0.1 as concentrated as that required for pH measurements of optimal stability.

**Materials for Kinetic Studies.**—Diphenyl disulfide was prepared in quantitative yield from benzenethiol and excess dimethyl sulfoxide by the method of Yiannios and Karabinos.[38]

β-Mercaptoethanol was distilled, bp 153° (749 mm), and stored under argon.

NEM was Aldrich purissima grace, mp 43.8–45.8°, homogeneous to thin layer chromatography on tlc grade silica gel, development with each of chloroform, benzene, acetone, ethyl acetate, or acetonitrile. *Anal.* Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64. Found: C, 57.53; H, 5.56.

Acetic acid for buffer preparations was dried by refluxing with acetic anhydride for 15 hr followed by fractionation. Potassium hydroxide was dissolved to 0.1 *N* in 95% ethanol, and the solution filtered prior to use for acetic acid–potassium acetate buffer preparations.

**Spectrophotometric Assay of NEM and Related Control Experiments.**—NEM was assayed at 302.0 nm (ε 700) (near its band maximum at 297.0 nm); absorption by arylthiols is low at 302.0 nm, usually $\epsilon_{ArSH} < 0.1\epsilon_{NEM}$. Ground-glass stoppered cuvettes prefilled with argon were used to minimize oxygen access and consequent disulfide formation and to allow rapid mixing by cell inversion so that the first OD measurements could be made at ≤10 sec after zero time.

Absence of solvolytic side reactions of NEM was established by control runs on NEM solutions. The constancy of OD at 302.0 nm over the duration of kinetic runs showed that solvolytic ring cleavage to produce *N*-ethylmaleamide or the amide ethyl ester which are transparent at 302.0 nm did not occur. This finding was confirmed by product analyses described later.

The addition products absorb at 302.0 nm ($\epsilon_{product} \cong 0.14$–$0.48 \times \epsilon_{NEM}$), and correction for this absorption was made in calculation of the NEM concentration, $(NEM)_t$, at any time *t*, from the expression $(NEM)_t = F(NEM)_0$ for $(ArSH)_0 > (NEM)_0$ and $(NEM)_t = (NEM)_0 - F(ArSH)_0$ for $(ArSH)_0 < (NEM)_0$ where $F = 1 - [(OD)_0 - (OD)_t]/[(OD)_0 - (OD)_\infty]$. The near coincidence of ε at 302.0 nm for NEM and α-(2-*tert*-butylphenylthio)-*N*-ethylsuccinimide prevented the use of the method described above. Instead the reaction was quenched at specific times by addition of 100 μl of β-mercaptoethanol. The $(NEM)_t$ was determined from the immediate OD decrease observed upon quenching.

**Amperometric Assay of Thiol and Related Control Experiments.**—Amperometric silver ion titrations of thiol[39] were performed for kinetic runs with benzenethiol to confirm that equimolar quantities of NEM and ArSH were consumed at any time *t* as assumed in the calculations of kinetic constants. The method used a rotating platinum wire indicator electrode, a saturated calomel reference electrode, and a Sargent manual polarograph, Model III, for current measurements. Calibration of the method using known weights of benzenethiol gave agreement within 1%.

Quenching for kinetic runs in which thiol was assayed was accomplished by addition of 50 ml of 1 *N* $H_2SO_4$ in 95% ethanol. The method was proved effective by prequenching of measured kinetic concentrations of thiol followed by addition of a kinetic concentration of NEM; three runs gave thiol titers which agreed within 1% with the thiol weights.

Diphenyl disulfide was shown not to react with silver ion under the titration conditions. A control experiment in which equimolar quantities of thiol and disulfide were used gave a titer within 1% of the thiol weight. Solutions of thiols delivered by the pipet technique employed for the kinetic runs and allowed to stand in stoppered cuvettes (preflushed with argon) for 15 min prior to silver ion titration gave thiol analyses within 1% of the values by weight. It was therefore concluded that no appreciable disulfide formation occurred during the periods of kinetic measurements.

Kinetic runs followed both by spectrophotometric NEM analyses and titrimetric thiol assays gave an average agreement of 2% for a series of 10 points.

**Product Analyses.**—Thin layer chromatographic analyses on tlc grade silica gel with each of a range of solvents (methylene chloride, chloroform, benzene, acetone, ethyl acetate, or acetonitrile) gave a single spot when equimolar amounts of reactants were employed. The reactions of NEM with 2-methylbenzenethiol and with 2-*tert*-butylbenzenethiol were carried out on a small preparative scale. The products isolated in quantitative yield without further purification were shown to correspond to the expected α-arylthio-*N*-ethylsuccinimides by nmr spectra and carbon and hydrogen analyses. *Anal.* Calcd for $C_{13}H_{15}NO_2S$ [α-(2-methylphenylthio)-*N*-ethylsuccinimide]: C, 62.64; H, 6.07. Found: C, 62.62; H, 6.04. Calcd for $C_{15}H_{21}NO_2S$ [α-(2-*tert*-butylphenylthio)-*N*-ethylsuccinimide]: C, 65.97; H, 7.27. Found: C, 66.13; H, 7.04.

**Temperature Control.**—All reactant solutions, cuvettes, and the spectrophotometer cuvette compartment were thermostated at 2.50 ± 0.2°.

**Buffer pH.**—All pH measurements were made at 25.0 ± 0.2° using a Copenhagen Radiometer pH meter no. 26 with always the same glass–calomel electrode pair standardized with two aqueous buffers; no corrections were made for the 95% ethanol–water junction potentials.

The pH range studied was 1.5 units. Measurements at higher and lower pH's were not feasible owing to solvolytic cleavage of NEM at higher pH and appreciable competition from disulfide formation due to the slower addition at lower pH. It was shown that the pH remained constant throughout the course of the reactions.

**Calculation of Kinetic Parameters.**—The kinetic parameters calculated are defined

$$d(\text{product})/dt = k_{obsd}(NEM)(ArSH) = k_{anion}(NEM)(ArS^-) \quad (5)$$

The $k_{obsd}$ values were determined from the standard integrated second-order expression and a least-squares regression programmed in FORTRAN IV for an IBM 360-91 computer. As

$$(ArS^-) = K_a(ArSH)/(H^+) \quad (6)$$

where $K_a$ is the apparent acid dissociation constant for thiol

$$k_{anion} = k_{obsd}(H^+)/K_a \quad (7)$$

Since measurements of $(H^+)$ and $K_a$ were made with the same electrodes, they include equal contributions from the 95% alcohol–water junction potential. Therefore, values of $k_{anion}$ calculated according to eq 7 should be accurate.

**Registry No.**—NEM, 128-53-0; α-(2-methylphenylthio)-*N*-ethylsuccinimide, 35740-35-3; α-(2-*tert*-butylphenylthio)-*N*-ethylsuccinimide, 35740-36-4.

**Acknowledgments.**—The author gratefully acknowledges the financial support of and helpful discussions with Dr. Paul D. Boyer. Dr. Donald C. Garwood assisted with the computer programs. Mr. Darryl Benson provided excellent technical assistance.

(38) C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).

(39) I. M. Kolthoff and W. E. Harris, *Ind. Eng. Chem., Anal. Ed.*, **18**, 161 (1946).

# Model Systems Related to Reactivity of Protein Sulfur Functions. II. The Effect of Hydrophobic Bulk on the Nucleophilicities of Alkyl-Substituted Benzenethiolate Anions toward Disulfide Bonds[1,2]

DOROTHY SEMENOW-GARWOOD* AND DONALD C. GARWOOD[3]

*The Department of Chemistry and Molecular Biology Institute, University of California, Los Angeles, California 90024*

*Received March 29, 1972*

The rates of cleavage of the sulfur–sulfur bond of ethyl 2,4-dinitrophenyl disulfide by a series of alkyl-substituted benzenethiolate anions in 95% ethanol at 25° are reported. Nucleophilic attack of ortho-substituted anions at sulfur is influenced by two steric effects: (1) rate acceleration due to inhibition of solvation of the reactant thiolate ion and (2) rate retardation due to steric repulsion between thiolate nucleophile and disulfide substrate. The first known example of net steric acceleration in cleavage of a disulfide bond due to hydrophobic bulk in the nucleophile is reported for *o-tert*-butylbenzenethiolate which is found to be five times as reactive as *p-tert*-butylbenzenethiolate. The effects of hydrophobic bulk in enzymic reactions involving mercaptide cleavage of disulfide bonds are discussed. The rate of sulfur–sulfur bond cleavage by benzenethiolate and *o-tert*-butylbenzenethiolate in reaction with ethyl-, 2-hydroxyethyl-, and 2-methoxyethyl-2′,4′-dinitrophenyl disulfide in 95% ethanol and in xylene at 25° are also reported. In 95% ethanol the order of reactivities for both thiolate anions parallels the inductive effects of H, HO, and $CH_3O$ groups. However, in xylene the order of rates for the 2-hydroxyethyl and the 2-methoxyethyl substrates is reversed. Two explanations of this result are considered: one steric (conformational freezing) and the other electronic (concomitant electrophilic catalysis by hydroxyl of the nucleophilic disulfide cleavage).

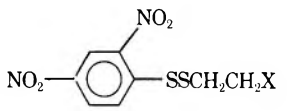
The factors which govern the reactivity of thiols toward disulfides have significance for several areas of biochemistry.[4,5] Among the most important are the use of the disulfide, 5,5′-dithiobis(2-nitrobenzoic acid),[6] as a probing reagent for protein sulfhydryl groups; thiol–disulfide exchanges between small molecule mercaptans and protein disulfide linkages which occur biochemically and are employed for chemical reduction of protein disulfide bonds;[7] intermolecular or intramolecular thiol–disulfide exchange between or within protein molecules such as albumins;[8-10] and reactions of protein thiol functions with disulfide linkages of substrates or cofactors such as proposed for the action of glutathione reductase[11] and lipoyl dehydrogenase.[12]

Although steric hindrance in the vicinity of the nucleophile[4,5] and positioning of catalytically crucial neighboring groups (*e.g.*, ficin[13] and streptococcal proteinase[14]) have been invoked to explain differential reactivities of protein thiol functions, investigations of these factors as they apply to mercaptide–disulfide displacements in model systems are almost entirely lacking.

Fava did observe severe rate retardation ($\sim 10^5$) for the exchange in aqueous solution of [$^{35}$S]sulfite ion with *tert*-butyl thiosulfate relative to ethyl thiosulfate[15] which is attributed to steric hindrance originating from the thiosulfate substrate. The even larger rate diminution ($\sim 10^6$) reported for the exchange of *tert*-butyl mercaptide ion with *tert*-butyl [$^{35}$S]disulfide in aqueous alcoholic solvents compared to the analogous *n*-butyl system[16] is probably predominantly due to steric hindrance arising from the disulfide substrate which obscures contributions from hydrophobic bulk in the mercaptide nucleophile.

Chan[17] has suggested participation by a protonated amino group in the cleavage by sulfite ion of postulated intermediate mixed disulfides of cysteine or β-aminoethyl mercaptan with proteinyl sulfur. McPhee[18] reported that introduction of a positive charge into a disulfide molecule greatly increased the rate of sulfitolysis.

We now report kinetic studies of the reactions in 95% ethanol of ethyl 2,4-dinitrophenyl disulfide (**1**) in



**1**, X = H
**2**, X = OH
**3**, X = $OCH_3$

buffered 95% ethanol with a series of alkyl-substituted benzenethiolate ($ArS^-$) anions selected for the purpose of assessing the influence of *hydrophobic bulk in the nucleophile*.

Similar measurements were made for the reaction of *each* of ethyl 2,4-dinitrophenyl disulfide (**1**), 2-hydroxyethyl 2′,4′-dinitrophenyl disulfide (**2**), and 2-methoxy-

(1) Supported in part by Grant No. GM 11094 from the Institute of General Medical Sciences, U. S. Public Health Service, and by Contract AT(04-3)-34, Project 102, of the U. S. Atomic Energy Commission; P. D. Boyer, Principal Investigator.

(2) (a) A preliminary report of a portion of this work has appeared: D. S. Garwood and D. C. Garwood, *Tetrahedron Lett.*, 4959 (1970). (b) Part I: D. S. Garwood, *J. Org. Chem.*, **37**, 3797 (1972).

(3) National Institutes of Health Special Research Fellow, 1969–1970.

(4) P. D. Boyer in "The Enzymes," Vol. 1, 2nd ed, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1959, p 511.

(5) R. Cecil in "The Proteins," Vol. 1, 2nd ed, H. Neurath, Ed., Academic Press, New York, N. Y., 1963, p 379.

(6) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

(7) F. G. Hopkins, *Biochem. J.*, **19**, 787 (1925).

(8) V. D. Hospelhorn, B. Cross, and E. V. Jensen, *J. Amer. Chem. Soc.*, **76**, 2827, 2830 (1954).

(9) W. Kauzmann, M. T. Watson, and H. K. Frensdorff, *ibid.*, **75**, 5157 (1953).

(10) C. B. Huggins, D. F. Tapley, and E. V. Jensen, *Nature (London)*, **167**, 592 (1951).

(11) C. E. Mize, T. E. Thompson, and R. G. Langdon, *J. Biol. Chem.*, **27**, 1596 (1962).

(12) V. Massey and C. Veeger, *Biochem. Biophys. Acta*, **40**, 184 (1960).

(13) M. R. Hollaway, A. P. Mathias, and B. R. Rabin, *ibid.*, **92**, 111 (1964).

(14) B. I. Gerwin, *J. Biol. Chem.*, **242**, 451 (1967).

(15) A. Fava and A. Iliceto, *J. Amer. Chem. Soc.*, **80**, 3478 (1958).

(16) A. Fava, A. Iliceto, and E. Camera, *ibid.*, **79**, 833 (1957).

(17) W. W. C. Chan, *Biochem.*, **7**, 4247 (1968).

(18) J. R. McPhee, *Biochem. J.*, **64**, 22 (1956).

ethyl 2′,4′-dinitrophenyl disulfide (**3**) with benzenethiolate and 2-*tert*-butylbenzenethiolate both in buffered (acetic acid–potassium acetate) 95% ethanol and in xylene containing the base 1,4-diazo[2.2.2]bicyclooctane (DABCO) in an effort to establish the occurrence of concomitant *intramolecular* electrophilic catalysis of the nucleophilic displacement. With the possible exception of the work of Chan[17] and McPhee[18] cited above, all previously reported examples of simultaneous electrophilic and nucleophilic catalysis of sulfur–sulfur bond scission have been *intermolecular* in nature, nucleophile, electrophile, and substrate each being initially separate molecular entities.[19]

## Results

The mechanism of the cleavage of disulfides by thiolate in a hydroxylic solvent SOH is depicted by eq 1 and 2.[16,20-23] The analysis of the kinetic data based upon this mechanism is described in the Experimental Section. Other reactions do not complicate the kinetic

$$\mathrm{ArSH} + \mathrm{SOH} \underset{\text{fast}}{\overset{K_a,\ \text{fast}}{\rightleftharpoons}} \mathrm{ArS^-} + \mathrm{SOH_2^+} \qquad (1)$$

$$\mathrm{ArS^-} + \mathrm{NO_2C_6H_3(NO_2)SSCH_2CH_2X} \underset{k_b}{\overset{k_{anion},\ \text{slow}}{\rightleftharpoons}} \mathrm{NO_2C_6H_3(NO_2)S^-} + \mathrm{ArSSCH_2CH_2X} \qquad (2)$$

analysis. Subsequent reaction of the product disulfide formed according to eq 2 with arenethiolate (eq 3) is

$$\mathrm{ArS^-} + \mathrm{ArSSCH_2CH_2X} \longrightarrow \mathrm{ArSSAr} + {}^-\mathrm{SCH_2CH_2X} \qquad (3)$$

expected to be negligibly slow since in all reactions studied $^-SCH_2CH_2X$ is a poor leaving group relative to arenethiolate.[20b,24,25] Indeed, analysis of reaction products showed the absence of symmetrical disulfide ArSSAr.

The observed rate constants for the reactions of alkyl-substituted benzenethiols (ArSH) with ethyl 2,4-dinitrophenyl disulfide (**1**) are summarized in Table I. In all cases, the fit of the data to the integrated expression for $k_{2,obsd}$ (integral of eq 15) is good with a standard deviation of points from the line of about 1% or less of the $k_{2,obsd}$ values. The rate constants for reaction of thiolate ($ArS^-$) with **1** (eq 2), $k_{2,anion}$, calculated from $k_{2,obsd}$ using eq 16, are also reported in Table I. The standard deviations for runs with a given alkylbenzenethiolate are from 0.5–5.6% of the average $k_{2,anion}$ values.

The $k_{2,anion}$ values for all $ArS^-$ species are comparable within a factor of two except for 2-*tert*-butylbenzenethiolate anion for which the $k_{2,anion}$ value is 8.5 times that for unsubstituted benzenethiolate. Since the rate-determining step (eq 2) involves nucleophilic attack of thiolate upon one of the sulfur atoms of the disulfide bond, the differences in $k_{2,anion}$ reflect the substituent effects upon the nucleophile.

The kinetic data for the reactions of benzenethiol and of 2-*tert*-butylbenzenethiol with 2-hydroxyethyl 2′,4′-dinitrophenyl disulfide (**2**) and with 2-methoxyethyl 2′,4′-dinitrophenyl disulfide (**3**) are reported in Table II for the reaction in 95% ethanol and in Table III for the reaction (in the presence of DABCO) in xylene. Since acid strengths were not available for the xylene medium, the observed rate constants for the molecular thiol species are reported. Thus, comparisons are made of observed $k$ values for a *given thiol* in a given solvent with each of the various disulfide molecules. Whereas in 95% ethanol the rates for the methoxy compound **3** are 1.3–1.5 times as great as for hydroxy compound **2**, in xylene the superiority is reversed with the rates for **2** found to be 2 to 3 times as fast as for **3**.

## Discussion

**Alkyl Substitution of the Nucleophile.**—An objective of the present investigation is to examine the effects of steric bulk introduced into the *nucleophile* upon the reaction of benzenethiolate anions with aryl alkyl disulfides. Studies of the effects of alkyl bulk in *charged* nucleophiles have not been reported previously. Rate retardation is an anticipated result since nonbonding repulsions will occur between a hindered nucleophile and the substrate in the transition state for sulfur–sulfur bond cleavage (eq 2). However, steric bulk in the anion will also inhibit solvent stabilization of the reactant thiolate, thereby increasing the rate of thiolate attack on sulfur. The current work was designed to examine the relative importance of these opposite effects of alkyl substituents.

To distinguish between the different electronic and steric substituent effects, a Brønsted correlation between rates of thiolate nucleophilic attack and thiolate basicity (or equivalently, thiol acidity) for the unhindered benzenethiols is employed here. If structural variation of the thiolate anion affects its nucleophilicity and its basicity comparably, the Brønsted plot produces a straight line whose slope (the Brønsted parameter $\beta$) measures the sensitivity of the disulfide cleavage reaction to the thiolate nucleophilicity. A Brønsted plot (Figure 1) of log $k_{2,anion}$ *vs.* $pK_a$ for four unhindered benzenethiols of Table I yields a $\beta$ value of 0.66 (standard deviation 0.03, correlation coefficient 0.99937).[26] Although the range of $pK_a$ values used to determine this estimate of $\beta$ is quite narrow, the value obtained is comparable to previously reported $\beta$ values of 0.53 for the reaction of a series of aliphatic thiols with thiamine *n*-propyl disulfide[20c] and 0.73 for similar aliphatic thiols in reaction with cystine.[27] The qualitative conclusions of the following discussion hold even in the unlikely event that the $\beta$ of this work is inaccurate by $\pm 0.15$.

(19) J. L. Kice, *Accounts Chem. Res.*, **1**, 58 (1968).

(20) (a) H. Nogami, J. Hasegawa, and N. Ikari, *Chem. Pharm. Bull.*, **15**, 685 (1967); (b) H. Nogami, J. Hasegawa, and N. Ikari, *ibid.*, **15**, 693 (1967); (c) H. Nogami, J. Hasegawa, N. Ikari, and K. Takeuchi, *ibid.*, **17**, 1541 (1969).

(21) L. Eldjarn and A. Pihl, *J. Biol. Chem.*, **225**, 499 (1957).

(22) T. Bersin and J. Steudel, *Chem. Ber.*, **71**, 1015 (1938).

(23) A. Fredga, *Arch. Chem. Mineral. Geol., Ser. A*, **12**, 13 (1937).

(24) A. Pihl and L. Eldjarn, *Proc. 4th Int. Congr. Biochem., 4th*, **13**, 43 (1958).

(25) A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3070 (1960).

(26) Owing to the physiological discomfiture experienced by all experimenters exposed to the thiols for extended periods, the series of thiols investigated was not enlarged beyond that reported in Table I.

(27) A. Pihl, L. Eldjarn, and K. F. Nakken, *Acta Chem. Scand.*, **12**, 1357 (1958).

TABLE I
SECOND-ORDER RATE CONSTANTS FOR REACTIONS OF ALKYL-SUBSTITUTED BENZENETHIOLS WITH ETHYL 2,4-DINITROPHENYL DISULFIDE IN 95% ETHANOL

| ArSH (Registry no.) | $(ArSH)_0 \times 10^4$ ($M$) | % reaction completion on which $k$ is based | $k_{obsd}$[a-c] ($M^{-1}$ sec$^{-1}$) | $k_{2,anion}$[a,c] $\times 10^{-4}$ ($M^{-1}$ sec$^{-1}$) |
|---|---|---|---|---|
| PhSH | 2.986 | 93 | 152.9 | 7.08 |
| (108-98-5) | 1.493 | 88 | 151.1 | 7.00 |
| | 0.9953 | 75 | 152.3 | 7.07 |
| | | | | Av[d] 7.05 ± 0.03 |
| 4-MePhSH | 1.071 | 67 | 115.2 | 12.65 |
| (106-45-6) | 0.5355 | 56 | 108.1 | 11.87 |
| | | | | Av[d] 12.26 ± 0.39 |
| 4-*tert*-BuPhSH | 2.620 | 87 | 117.2 | 11.53 |
| (2396-68-1) | 2.059 | 86 | 121.7 | 11.98 |
| | 1.310 | 82 | 115.7 | 11.39 |
| | | | | Av[d] 11.63 ± 0.25 |
| 3-MePhSH | 1.527 | 75 | 129.6 | 10.01 |
| (108-40-7) | 1.018 | 62 | 127.0 | 9.82 |
| | 0.7634 | 60 | 126.0 | 9.74 |
| | | | | Av[d] 9.86 ± 0.41 |
| 2-MePhSH | 3.065 | 83 | 53.7 | 11.04 |
| (137-06-4) | 1.532 | 69 | 47.3 | 9.71 |
| | 1.226 | 69 | 48.6 | 9.98 |
| | | | | Av[d] 10.24 ± 0.5 |
| 2,6-DiMePhSH | 15.82 | 87 | 12.8 | 9.25 |
| (118-72-9) | 7.909 | 85 | 13.0 | 9.40 |
| | 5.273 | 84 | 13.3 | 9.63 |
| | | | | Av[d] 9.43 ± 0.16 |
| 2-*tert*-BuPhSH | 40.08 | 99 | 11.4 | 61.3 |
| (19728-41-7) | 20.04 | 95 | 11.0 | 59.2 |
| | 10.02 | 90 | 11.1 | 59.7 |
| | | | | Av[d] 60.1 ± 0.90 |
| 2,4,6-Tri-*tert*-BuPhSH | 46.76 | 24 | 0.134[e,f] | 12.2[e,g] |
| (961-39-7) | 35.52 | 16 | 0.139[e,f] | 12.7[e,g] |
| | | | | Av[d] 12.4 ± 0.4 |

[a] Temperature, 25.0 ± 0.2°. [b] pH 6.91 measured as described in Experimental Section. [c] All initial disulfide concentrations were $4.57 \times 10^{-5}$ $M$ unless otherwise specified. [d] Average ± standard deviation. [e] Initial disulfide concentration was $6.11 \times 10^{-5}$ $M$. [f] Back-reaction not taken into account. [g] Based on value for $pK_a$ of 12.87 estimated as described in Experimental Section.

TABLE II
SECOND-ORDER RATE CONSTANTS FOR REACTIONS OF ARSH WITH 2-SUBSTITUTED ETHYL 2′,4′-DINITROPHENYL DISULFIDES IN 95% ETHANOL

| ArSH | Disulfide | $(ArSH)_0 \times 10^5$ ($M$) | % reaction completion on which $k$ is based | $k_{2,obsd}$[a-c] ($M^{-1}$ sec$^{-1}$) |
|---|---|---|---|---|
| PhSH | 2 | 16.06 | 94 | 343 |
| | | 8.45 | 79 | 323 |
| | | 5.35 | 68 | 334 |
| | | | | Av[d] 333 ± 10 |
| PhSH | 3 | 16.90 | 95 | 435 |
| | | 8.45 | 85 | 427 |
| | | 5.63 | 74 | 418 |
| | | | | Av[d] 427 ± 9 |
| 2-*tert*-BuPhSH | 2 | 10.02 | 63 | 25.2 |
| | | 5.01 | 75 | 27.8 |
| | | | | Av[d] 26.5 ± 1.8 |
| 2-*tert*-BuPhSH | 3 | 10.02 | 64 | 39.6 |
| | | 5.01 | 62 | 38.9 |
| | | | | Av[d] 39.2 ± 0.5 |

[a] Temperature, 25.0 ± 0.2°. [b] pH 6.75 measured as described in Experimental Section. [c] All initial disulfide concentrations were $4.58 \times 10^{-5}$ $M$. [d] Average ± standard deviation.

The free energy of activation for thiolate cleavage of a disulfide bond may be separated into three major components as in eq 4: (1) the free-energy change resulting from the adjustment of solvation on going from reactants to the transition state, (2) the free-energy change due to changes in electronic interactions and bond reorganization, and (3) the free-energy change due to differences in nonbonding repulsions upon going from separated reactants to the transition state.

$$\Delta F^{\pm} = \Delta F^{\pm}_{solvation} + \Delta F^{\pm}_{electronic} + \Delta F^{\pm}_{steric} \quad (4)$$

The effect of substitution on $\Delta F^{\pm}$, $\delta_R \Delta F^{\pm}$, is given by the difference in substituent effects on the transition state (TS) and upon the ground state (GS) as shown in eq 5. If only the thiolate substituent is varied while

$$\delta_R \Delta F^{\pm} = \delta_R F^{TS} - \delta_R F^{GS} \quad (5)$$

the disulfide substrate remains the same, $\delta_R F^{GS}$ becomes $\delta_R F^{anion}$.

In the first paper of this series[1b] it was shown that, for the ortho-substituted benzenethiols of interest, hindered thiols were less acidic than related unhindered thiols owing to steric inhibition of solvation of ortho-substituted thiolate anions. It was argued that, to a good approximation, nonbonding repulsions within the thiolate anion itself could be neglected. Under this condition eq 6 holds approximately. Since substituent

$$\delta_R F^{anion} \approx \delta_R F^{anion}_{solvation} + \delta_R F^{anion}_{electronic} \quad (6)$$

effects on the free energy of the *parent* (un-ionized) alkylbenzenethiol are expected to be small compared to the effects on the thiolate anion, the relative $pK_a$'s of

TABLE III
THIRD-ORDER RATE CONSTANTS FOR REACTIONS OF BENZENETHIOLS WITH 2-SUBSTITUTED ETHYL 2',4'-DINITROPHENYL DISULFIDE IN XYLENE

| ArSH | Disulfide | $(ArSH)_0 \times 10^4$ ($M$) | $(DABCO)_0 \times 10^3$ ($M$) | % reaction completion on which $k$ is based | $k_{3,obsd}$[a,b] ($M^{-2}$ sec$^{-1}$) |
|---|---|---|---|---|---|
| PhSH | 1 | 15.96 | 7.40 | 35 | 530 |
| | | 7.98 | 3.70 | 16 | 518 |
| | | | | | Av[c] 524 ± 8 |
| PhSH | 2 | 15.96 | 7.40 | 70 | 3073 |
| | | 7.98 | 3.70 | 49 | 2946 |
| | | 7.98 | 3.70 | 42 | 3093 |
| | | | | | Av[c] 3044 ± 80 |
| PhSH | 3 | 15.96 | 7.40 | 42 | 1019 |
| | | 7.98 | 3.70 | 23 | 1003 |
| | | | | | Av[c] 1011 ± 11 |
| 2-*tert*-BuPhSH | 1 | 50.91 | 120.1 | 64 | 87.8 |
| | | 25.51 | 57.1 | 57 | 80.9 |
| | | 25.45 | 60.0 | 41 | 74.4 |
| | | | | | Av[c] 81.0 ± 6.7 |
| 2-*tert*-BuPhSH | 2 | 25.45 | 60.0 | 62 | 245.1 |
| | | 12.75 | 57.1 | 58 | 255.0 |
| | | | | | Av[c] 250.0 ± 7.0 |
| 2-*tert*-BuPhSH | 3 | 25.51 | 115.9 | 65 | 120.8 |
| | | 25.45 | 60.0 | 57 | 123.8 |
| | | 12.75 | 57.9 | 48 | 105.5 |
| | | | | | Av[c] 116.7 ± 9.3 |

[a] Temperature, 25.0 ± 0.2°. [b] All initial disulfide concentrations were $4.58 \times 10^{-5}$ $M$. [c] Average ± standard deviation.

the substituted benzenethiols provide reasonable relative measures of $\delta_R F^{anion}$. Therefore, $\delta_R F^{GS}$ (eq 5) will be approximately linearly related to the $pK_a$ of the thiol. Any significant deviations of log $k_{2,anion}$ from linearity with $pK_a$ for hindered benzenethiolates in a Brønsted plot may consequently be ascribed to substituent effects on the transition state, *i.e.*, on $\delta_R F^{TS}$. Similar interpretations have been reported for the addition of alkylbenzenethiols to *N*-ethylmaleimide.[2b]

The rate-determining step (eq 2) involves formation of a new bond between the thiolate sulfur and one of the disulfide sulfur atoms. Consequently, for hindered (ortho substituted) benzenethiolates the alkyl bulk proximate to thiolate sulfur is expected to cause deviations from the extrapolated linear Brønsted plot of Figure 1 owing principally to steric repulsions between the nucleophile and the substrate (*i.e.*, $\delta_R F^{TS}_{steric}$). Inductive effects may partially cancel between GS and TS and, in any case, should parallel $pK_a$ rather than contribute to deviations from linearity. Therefore, such deviations will be interpreted as measures of steric repulsion.

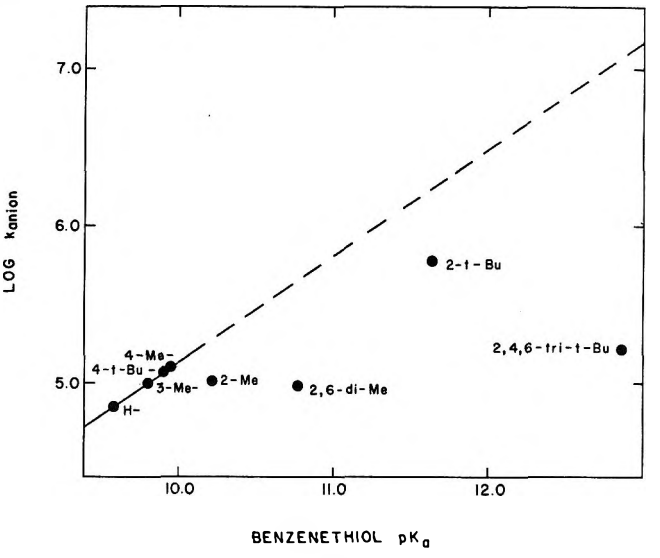



Figure 1.—Brønsted plot for reaction of alkyl-substituted benzenethiolate with ethyl 2,4-dinitrophenyl disulfide.

The results for reaction of *o*-methyl-substituted benzenethiolates with 1 as plotted in Figure 1 do suggest a small rate retardation of a factor of 1.8 due to steric repulsion between the nucleophile and the disulfide. Consistent with this interpretation, the retardation is more pronounced for two *o*-methyl groups which give a rate retardation from the predicted rate by a factor of ~8.

In the case of *o*-*tert*-butyl substitution, the predominance of the effect in which steric hindrance to solvation of the thiolate anion increases its nucleophilicity leads to a marked acceleration of the rate of cleavage by a factor of 5 relative to the para isomer (Table I). This is the first reported example of rate acceleration in a nucleophilic substitution attributable to decreased solvation resulting from steric bulk in the nucleophile. The rate increment predicted solely for this effect is (from Figure 1) a factor of 15 over the rate for 4-*tert*-butylbenzenethiolate, but this increment is reduced to the observed relative rate as a consequence of a decelerating factor of ~3 apparently caused by steric crowding in the transition state. Furthermore, increased steric repulsion between reactants which results upon introduction of a second *o*-*tert*-butyl group reduces the net rate to a value comparable to that of the methyl-substituted benzenethiols (compare $k_{2,anion}$ for 2,4,6-tri-*tert*-butylbenzenethiolate, Table I). Again, the Brønsted plot of Figure 1 provides an estimate of the contribution of steric repulsion between the nucleophile and the substrate to the net rate. The steric retardation factor of 3 for 2-*tert*-butylbenzenethiol compares with the corresponding factors of 1.8 and 8

for 2-methyl- and 2,6-dimethylbenzenethiolates, respectively. The two *o-tert*-butyl groups of 2,4,6-tri-*tert*-butylbenzenethiolate cause a rate retardation below that predicted from basicity alone by a factor of 72. In this case, severe steric repulsion between reactants in the transition state outweighs the increased thiolate nucleophilicity owing to anion desolvation.

The above results have clear implications for enzymic reactions between mercaptide groups and disulfide linkages. The nucleophilicity of the mercaptide function can be increased to a point by adjacent hydrophobic side chains. However, too severe crowding of the mercaptide will interfere with attack on the disulfide bond. An optimum degree of hydrophobic shielding can produce enhanced rates. These results further support the suggestions[4,5] that differences in hydrophobic environments explain the differential reactivities of protein thiol functions.

**Electrophilic Catalysis of Nucleophilic Cleavage of the Disulfide Bond.**—The rates of sulfur–sulfur bond cleavage in 2-hydroxyethyl 2′,4′-dinitrophenyl disulfide (**2**) and related ethyl (**1**) and 2-methoxyethyl (**3**) disulfides by thiolate nucleophiles in the dissociating solvent 95% ethanol (Table II) and in the nondissociating solvent *m*-xylene (Table III) were studied to ascertain the effects of an intramolecular hydroxyl group.

In 95% ethanol, the methoxyethyl disulfide **3** is slightly more reactive than the corresponding hydroxyethyl compound **2** with both unhindered (benzene-) and hindered (2-*tert*-butylbenzene-) thiolate nucleophiles by factors of 1.3 and 1.5, respectively (Table IV).

TABLE IV

COMPARISON OF SUBSTITUENT EFFECTS FOR REACTION OF 2-SUBSTITUTED ETHYL 2′,4′-DINITROPHENYL DISULFIDE WITH BENZENETHIOLS IN 95% ETHANOL

| | | | $k_{obsd}$ | |
|---|---|---|---|---|
| Compd | Ethyl substitutent | $\sigma_I$[a] | For PhSH | For 2-*tert*-BuPhSH |
| 1 | H | 0.00 | 152 | 11.2 |
| 2 | HO | 0.05 | 333 | 26.5 |
| 3 | $CH_3O$ | 0.07 | 427 | 39.5 |

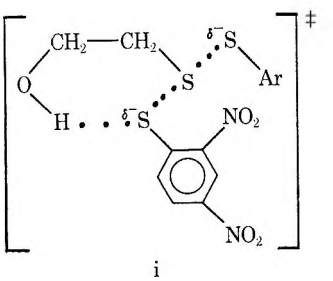
[a] Inductive $\sigma$ constant for $XCH_2$ [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)].

These small differences in rates are due primarily to inductive effects of the oxyalkyl function as shown by the fact that the observed rates for ethyl, 2-hydroxyethyl-, and 2-methoxyethyl systems in this solvent are in the same order as the inductive substituent constants $\sigma_I$ of $CH_3$, $HOCH_2$, and $CH_3OCH_2$ groups.

Indications of intramolecular hydrogen bonding to the leaving group were absent, as was expected, since in a hydrogen-bonding solvent such as 95% ethanol, the substrate intramolecular hydroxyl is solvated and cannot compete with solvation of the leaving group by solvent.

In the aprotic solvent xylene, the reversal of the rates for the oxy compounds was observed. Table III shows that **3** is *slower* than **2** by factors of 3 and 2 for benzenethiol and 2-*tert*-butylbenzenethiol, respectively. Both disulfides **2** and **3** are still cleaved faster than the parent disulfide **1**.

The greater reactivity of the 2-hydroxy compound was expected in the aprotic solvent since this system permits formation of a six-membered-ring transition



i

state (i) in which intramolecular hydrogen bonding of the leaving group by the hydroxyl hydrogen can occur. The polar character of the hydrogen can assist the cleavage by electrophilic catalysis and/or the hydrogen bonding can hold the substrate in a favorable conformation for attack by the nucleophilic species.[28] Clearly these rate enhancing effects are precluded in the methoxy substrate **3** since the hydrogen of **2** has been replaced by a methyl group.

Thus, although the electrophilic catalysis interpretation of the results in xylene is not uniquely required by the data, the results are in accord with such an explanation. Except for similar participation posited during a step of sulfonation of protein SH groups,[17] these results provide the first specific experimental support of *the possibility* of concomitant electrophilic and nucleophilic catalysis of disulfide bond cleavage in models for biological systems.[19] Although the rate factor attributable to intramolecular electrophilic catalysis is small for the 2-hydroxyethyl system (a factor of ~3 or 4 when corrected for inductive effects), more favorable or precise positioning in enzymic systems of an electrophilic group (including the possibility of $NH_3^+$ as well as OH) with respect to the disulfide bond being cleaved may contribute a marked rate enhancement.

## Experimental Section

**Materials.**—The arylthiols used were obtained, purified, and characterized as previously described[1b] except for 2,4,6-tri-*tert*-butylbenzenethiol which was the generous gift of Dr. Wolfgang Rundel. Commercial 1,4-diazo[2.2.2]bicyclooctane (DABCO) was purified by sublimation. Solvent *m*-xylene was reagent grade and was transparent in the region of spectral measurements.

**Buffer.**—Acetic acid–potassium acetate buffer in 95% ethanol was prepared as previously described.[1b]

**Ethyl 2,4-Dinitrophenyl Disulfide** (**1**).—Ethyl 2,4-dinitrophenyl disulfide was prepared in quantitative yield from the reaction of ethanethiol with 2,4-dinitrobenzenesulfenyl chloride in glacial acetic acid by the method of Parker and Kharasch.[25] Recrystallization of the product once from acetic acid, then twice from absolute ethanol, gave yellow needles, mp 86.0–86.5°. *Anal.* Calcd for $C_8H_8N_2O_4S_2$: C, 36.93; H, 3.10. Found: C, 36.97; H, 3.00.

**3-Hydroxyethyl 2′,4′-Dinitrophenyl Disulfide** (**2**).—The compound 2-hydroxyethyl 2′,4′-dinitrophenyl disulfide was prepared in quantitative yield from 2-hydroxyethanethiol and 2,4-dinitrophenylsulfenyl chloride as previously described[25] except that carbon tetrachloride was used instead of acetic acid solvent to prevent acetylation. Recrystallization four times from aqueous methanol gave yellow needles, mp 108.1–108.6°. *Anal.* Calcd for $C_8H_8N_2O_5S_2$: C, 34.77; H, 2.91. Found: C, 34.81; H, 2.85.

**2-Methoxyethyl 2′,4′-Dinitrophenyl Disulfide** (**3**).—The compound 2-methoxyethyl 2′,4′-dinitrophenyl disulfide was prepared in quantitative yield from 2-methoxyethanethiol and 2,4-dinitrobenzenesulfenyl chloride by the method described for **2**

(28) For the reaction in the solvent xylene of low dielectric constant (2.4), the nucleophilic species is the ammonium–thiolate ion pair rather than a dissociated thiolate ion. See B. Dmuchovsky, B. D. Vineyard, and B. Zienty, *J. Amer. Chem. Soc.*, **86**, 2874 (1964).

above. Recrystallization three times from absolute ethanol gave yellow needles, mp 78.4–79.0°. *Anal.* Calcd for $C_9H_{10}N_2O_6S_2$: C, 37.24; H, 3.47. Found: C, 37.38; H, 3.48.

**2-Methoxyethanethiol.**—2-Methoxyethanethiol was prepared in 70% yield by alkaline hydrolysis in methanol of 2-methoxyethyl thioacetate. The latter compound was prepared in 95% yield from 2-methoxyethyl *p*-toluenesulfonate and the potassium salt of thiolacetic acid by the method of Chapman and Owen;[29] its structure was established by ir and nmr spectra.

**Kinetics. Spectrophotometric Assay of Product 2,4-Dinitrobenzenethiolate Anion from Thiol–Disulfide Reactions.**—The product thiolate was assayed at $\lambda_{max}$ 425 nm ($\epsilon$ 1.90 × $10^4$ in 95% ethanol and 1.85 × $10^4$ in *m*-xylene). The reactants and product disulfides at the concentrations used do not absorb appreciably at 425 nm. Ground-glass-stoppered cuvettes prefilled with argon were used to minimize facile air oxidation of the chromophoric product to the transparent symmetrical disulfide and to allow rapid mixing so that the first OD measurements could be made at ≤10 sec after zero time. All solution vessels and pipets were preflushed and filled with argon. Solutions of 2,4-dinitrobenzenethiolate anion were shown to maintain a constant optical density over time periods equal to total reaction times.

**Control Experiments.**—All disulfide reactants were shown to be stable to heating in the reaction solvent and to irradiation with light of wavelength greater than 250 nm at room temperature.

In the xylene reactions it was established that the arenethiols failed to yield any chromophoric product when placed with the disulfide (**1**–**3**) in the absence of DABCO. Similarly the disulfides plus DABCO did not generate the colored product unless the thiol was present.

**Product Analyses.**—Thin layer chromatographic analysis on tlc grade silica gel were performed on the products of the thiol–disulfide runs in both 95% ethanol and xylene. In every case development with each of methylene chloride, chloroform, benzene, acetone, ethyl acetate, or acetonitrile showed no mixed disulfide between starting thiol and 2,4-dinitrobenzenethiol or symmetrical disulfide from the starting thiol; the only disulfides present were a small quantity of the starting disulfide and a major proportion of the mixed disulfide of the original thiol and the aliphatic portion of the original disulfide.

That the reaction product was essentially all in the chromophoric 2,4-dinitrobenzenethiolate form at the pH of 6.91 used for the kinetic runs was shown by the failure of optical density to increase when pH was raised above 6.91. This finding is in accord with a p$K_a$ for 2,4-dinitrobenzenethiol estimated to be <4 in 95% ethanol at 25° according to the method of Barlin and Perrin.[30]

**Temperature Control.**—All reactant solutions, cuvettes, and the spectrophotometer cuvette compartment were thermostated at 25.0 ± 0.2°.

**Buffer pH.**—All pH measurements were made at 25.0 ± 0.2° using a Copenhagen Radiometer pH meter no. 26 with always the same glass–calomel electrode pair standardized with two aqueous buffers; no corrections were made for the 95% ethanol/water junction potential. It was shown that pH decrease over the course of the reaction was limited to ≤0.04 pH units.

**Calculation of Kinetic Parameters.**—The observed second-order rate constants, $k_{2,obsd}$, based on the concentrations of the neutral arenethiol species (ArSH), for reactions with disulfides (DIS) in 95% ethanol to give the products 2,4-dinitrobenzenethiolate ion ($P_1$) and new mixed alkyl aryl disulfide ($P_2$), were obtained from the following kinetic analysis which corrects for the back-reaction whose specific rate constant is $k_{2,b}$ (eq 7).

$$\mathrm{ArSH} + \mathrm{DIS} \underset{k_{2,b}}{\overset{k_{2,obsd}}{\rightleftharpoons}} P_1 + P_2 \qquad (7)$$

When the equilibrium depicted in eq 7 is attained, and $(P_1)$ is equal to $(P_2)$ at all reaction times as is true for our case, then the forward and reverse reaction rate constants are given by

$$k_{2,obsd}/k_{2,b} = (P_1)_e^2/(\mathrm{ArSH})_e(\mathrm{DIS})_e \qquad (8)$$

where the subscript e designates an equilibrium concentration. $(P_1)_e$ is determined from the OD at 425 mμ at reaction completion. The equilibrium concentrations of thiols and disulfides are given by

$$(\mathrm{ArSH})_e = (\mathrm{ArSH})_0 - (P_1)_e \qquad (9)$$

and

$$(\mathrm{DIS})_e = (\mathrm{DIS})_0 - (P_1)_e \qquad (10)$$

where 0 subscripts indicate initial concentrations. Thus, $k_{2,b}$ can be expressed in terms of $k_{2,obsd}$, the initial and equilibrium concentrations according to eq 11. The assayed rate of forma-

$$k_{2,b} = k_{2,obsd}[(\mathrm{ArSH})_0 - (P_1)_e][(\mathrm{DIS})_0 - (P_1)_e]/(P_1)_e^2 \qquad (11)$$

tion of $P_1$ is given by

$$d(P_1)/dt = k_{2,obsd}(\mathrm{ArSH})(\mathrm{DIS}) - k_{2,b}(P_1)^2 \qquad (12)$$

Also

$$(\mathrm{ArSH}) = (\mathrm{ArSH})_0 - (P_1) \qquad (13)$$

$$(\mathrm{DIS}) = (\mathrm{DIS})_0 - (P_1) \qquad (14)$$

Substituting in eq 12 in terms of equations 11, 13, and 14, we obtain the readily integrable differential expression 15 for the rate of formation of $P_1$.

$$\frac{1}{k_{2,obsd}}\frac{d(P_1)}{dt} = (\mathrm{ArSH})_0(\mathrm{XDIS})_0 - [(\mathrm{ArSH})_0 + (\mathrm{XDIS})_0](P_1) + [(\mathrm{ArSH})_0(P_1)_e + (\mathrm{XDIS})_0(P_1)_e - (\mathrm{ArSH})_0(\mathrm{XDIS})_0]\frac{(P_1)^2}{(P_1)_e^2} \qquad (15)$$

Values of $k_{2,obsd}t$ were calculated for each kinetic point from the integrated expression. A least-squares linear regression applied to $k_{2,obsd}t$ *vs.* the time $t$ gave in all cases good straight lines of slope $k_{2,obsd}$.

The integrated rate expression was programmed in FORTRAN IV for an IBM 360-91 computer.

Kinetic parameters calculated from initial rate data by a method which neglected the back-reaction differed by ≤5% from values corrected for back-reaction. Neglect of back-reaction was necessary in the 2,4,6-tri-*tert*-butylbenzenethiol case where the relatively slow reaction precluded a stable equilibrium OD owing to oxidation of the chromophoric product anion.

The rate constant for the actual nucleophile, thiolate anion, ($k_{2,anion}$) was obtained according to eq 16; the validity of this method has been described previously.[2b]

$$k_{2,anion} = k_{2,obsd}\frac{(H^+)}{K_a} \qquad (16)$$

The acidity constant values used were those previously reported[2b] except for 2,4,6-tri-*tert*-butylbenzenethiol for which the low solubility in 95% ethanol precluded p$K_a$ measurements by the method used for the other arenethiols. The p$K_a$ of the 2,4,6-tri-*tert*-butyl derivative was estimated as 12.87 from the value for 2,4,6-tri-*tert*-butylphenol (p$K_a$ = 17.62 in methanol at 25°)[31] since an excellent correlation exists between the p$K_a$'s of alkyl substituted phenols in methanol and the corresponding thiols in 95% ethanol.[32]

$$pK_a^{ArOH} = 0.983\ pK_a^{ArSH} + 4.97 \qquad (17)$$

For the reactions conducted in xylene a different kinetic analysis was used. The expected third-order kinetics, first order in each of three different reactants (ArSH, DIS, and DABCO), introduces considerable complexity into integration of the appropriate rate expression. A simpler procedure is to obtain the third-order rate constant $k_{3,obsd}$ from the pseudo-first-order rate constant $k_{1,obsd}$ defined by

$$k_{1,obsd}t = -\ln\frac{(\mathrm{DIS})_0 - (P)}{(\mathrm{DIS})_0} \qquad (18)$$

where $(\mathrm{DIS})_0$ is the initial disulfide concentration and (P) is the concentration of product chromophoric anion. A least-squares linear regression is applied to the initial portion of the rate data

(29) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950).
(30) G. B. Barlin and D. D. Perrin, *Quart. Rev.*, **20**, 75 (1966).
(31) C. H. Rochester and B. Rossall, *Trans. Faraday Soc.*, **65**, 1004 (1969).
(32) See footnote 3 of ref 28.

which yields a value for $k_{1,obsd}$ that is invariant with time within experimental error. Then,

$$k_{3,obsd} = k_{1,obsd}/(DABCO)_0(ARSH)_0 \quad (19)$$

where $(DABCO)_0$ and $(ArSH)_0$ are the initial concentrations of base and thiol, respectively. The procedure is particularly successful for these rate data because both the base and thiol concentrations exceed the disulfide concentrations by a factor of at least 40, and therefore remain essentially constant throughout all runs.

The integrated rate expression was programmed in FORTRAN IV for an IBM 360-91 computer.

Acidity data were not available for the thiols in xylene solution; so rate constants for the anionic species were not determined. Rather comparisons were made of $k_{3,obsd}$ values for a single thiol on the various disulfides (1–3).

**Registry No.**—1, 22057-41-6; 2, 955-59-9; 3, 35740-31-9.

**Acknowledgment.**—The authors gratefully acknowledge the financial support of and helpful discussions with Dr. Paul D. Boyer. Mr. Darryl Benson provided excellent technical assistance.

# Reactions of Sulfur Diimides with Ketenes

TORU MINAMI,* KAZUNORI YAMATAKA, YOSHIKI OHSHIRO, TOSHIO AGAWA, NORITAKE YASUOKA, AND NOBUTAMI KASAI

*Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka, 565, Japan*

*Received March 31, 1972*

The reaction products of sulfur diimides **1** with diphenylketene (**2a**) are temperature dependent. The reaction of diphenylsulfur diimide (**1a**) with **2a** at 6–8° gave the 1,2 cycloadduct **4** and at 80° the 1,1 cycloadduct **6a**. Refluxing **4** in benzene led to **6a** and **2a**. In contrast to **1a**, di-*tert*-butylsulfur diimide (**1b**) and **2a** at 0–2° gave 1,2 cycloadduct **3b**, which readily underwent rearrangement to **6b** under hexane reflux. The reaction of sulfur diimides **1** with alkylketenes gave no 1,2 or 1,3 cycloadducts but the thiobisamine derivatives **23** or **24** or their hydrolysis products. The reaction between diphenylsulfur diimide (**1a**) and dimethylketene (**2c**) gave rise to 2-phenylimino-3,3-dimethyl-1*H*-2,1-benzothiazin-4(3*H*)-one (**27a**) in addition to *N*,*N*′-diphenyl-*N*-(2-methylpropenoyl)-*N*′-isobutanoyl thiobisamine (**24b**).

Some studies on the reaction of sulfur diimides with diphenylketene have recently been reported. In our previous communication,[1] the structure of the product from diphenylsulfur diimide (**1a**) and diphenylketene (**2a**) was assumed to be 1-phenylimino-2,4,4-triphenyl-1,2-thiazetidin-3-one (**3a**) on the basis of ir, mass spectrum, and some chemical properties. An X-ray structure investigation,[2] however, showed that the structure is 2,4,4,5-tetraphenyl-1,2,5-thiadiazolidin-3-one (**6a**) instead of **3a**. The result is in accordance with the reported reaction of di-*p*-ethoxycarbonylphenylsulfur diimide with diphenylketene (**2a**).[3]

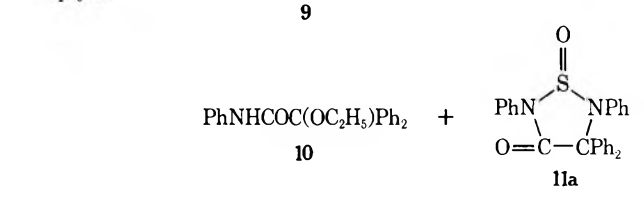
On the other hand, Kresze and Grill[4] isolated from the reaction of di-*p*-toluenesulfonylsulfur diimide with **2a** a 1-imino-1,2-thiazetidin-3-one derivative, which was easily isomerized to the 1,2,5-thiadiazolidin-3-one. Thus, variations in the sulfur diimide resulted in the formation of two types of 1,1 cycloadducts.

We have studied whether or not **6a** is formed *via* **3a** in analogy to Kresze's result.[4] Further, we report the reaction of various alkylketenes with sulfur diimides.

## Part A

### Results and Discussion

**Reaction of Diphenylsulfur Diimide with Diphenylketene.**—The reaction between diphenylsulfur diimide (**1a**) and diphenylketene (**2a**) in refluxing benzene gave the 1,3 cycloadduct, 2,4,4,5-tetraphenyl-1,2,5-thiadiazolidin-3-one (**6a**) in 67% yield. The reaction at lower temperature (6–8°), however, afforded only an unstable cycloadduct **4**. The yield of **4** was dependent on the molar ratio of **1a** to **2a** used in the reaction. The reaction using **1a** in double the molar quantity of **2a** gave **4** in 75% yield, while equimolar amounts produced **4** in 32% yield together with recovered **1a** (24%). On the other hand, refluxing an equimolar mixture of **4** and **1a** in benzene led to only **6a** (76%). With refluxing ethanol, **4** gave **6a** (44%), diphenylacetic acid ethyl ester (**9**) (38%), 1-ethoxy-1,1-diphenylacetanilide (**10**) (27%), and 2,4,4,5-tetraphenyl-1,2,5-thiadiazolidin-3-one 1-oxide (**11a**) (11%).




The unstable cycloadduct **4** contains 1 mol of **1a** and 2 mol of **2a** by elemental analysis, although the mass spectrum of **4** does not show any peak above the fragment ion peak at *m/e* 408 corresponding to the elimination of **2a** from the molecular ion. The ir spectrum of **4** exhibits carbonyl, carbon–carbon double bond, and ether absorptions at 1685, 1625, and 1275 $cm^{-1}$, respectively.

The chemical degradation and the physical data above do not clearly establish the structure of **4**. Accordingly, the structure was determined by X-ray analysis to be 2,3,4,6,7-pentahydro-2,4,4,7-tetraphenyl-3-oxo-1,5,2,7-thiaoxadiazepin-6-ylidenediphenylmethane. The molecular structure of **4** is shown in Figure 1.

Its formation would be rationalized in terms of one of two possible paths (path A and path B). As outlined in Scheme I, path A can be accounted for by a sequence of cycloaddition (**3a**), ring opening to the di-

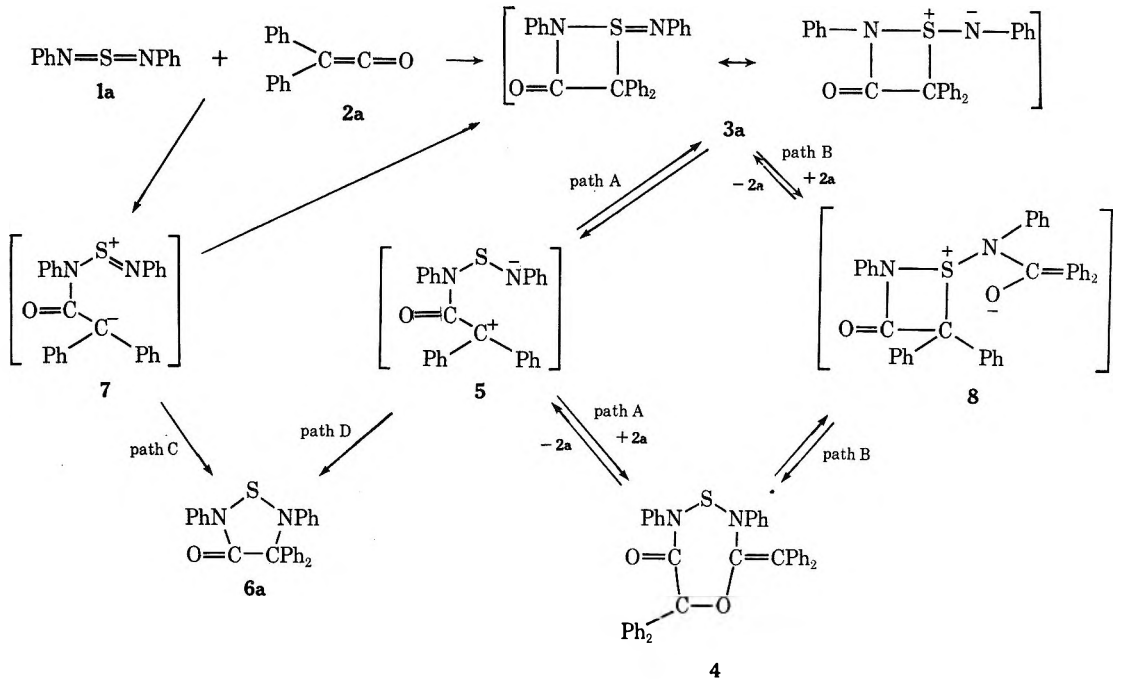
(1) T. Minami, O. Aoki, H. Miki, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, 447 (1969).

(2) N. Yasuoka, N. Kasai, T. Minami, Y. Ohshiro, T. Agawa, and M. Kakudo, *Bull. Chem. Soc. Jap.*, **43**, 1905 (1970).

(3) H. H. Hörhold and H. Eibisch, *Tetrahedron*, **25**, 4277 (1969).

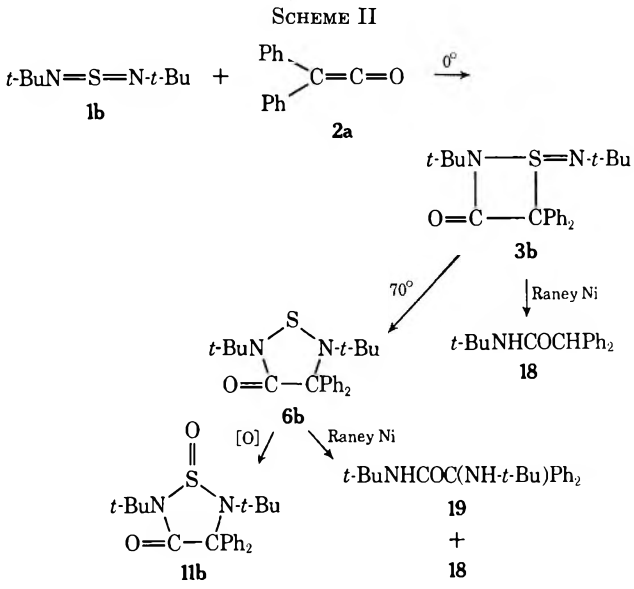
(4) H. Grill and G. Kresze, *Tetrahedron Lett.*, 1427 (1970).

SCHEME I



polar acyclic adduct **5**, and the addition of a second molecule of **2a** to **5**, while path B is explicable by the addition of one more molecule of **2a** to **3a** to give **8**, followed by ring opening and cyclization. As shown in Scheme II, a 1,2 cycloadduct from **2a** and di-*tert*-

SCHEME II



butylsulfur diimide undergoes readily ring opening to a 1,3 cycloadduct but does not react with **2a**. The 1,2 cycloadduct from **2a** and di-*p*-toluenesulfonylsulfur diimide shows the similar chemical property.[4] These results suggest that ring opening is easier than the addition of **2a** to the 1,2 cycloadducts. Therefore, ring opening of **3a** would similarly take place rather than the addition of **2a** to **3a**. Since the formation of **4** cannot be explained by 1,5 cycloaddition of **7** across the C=O double bond of a second molecule of **2a**, ring opening of **3a** to **5**, followed by the addition of **2a**, must occur.

For the formation mechanism of **6a** from **1a** and **2a** at high temperature, two possible paths (path C and path D) are conceivable. Since it is reasonable to consider that products **4** and **6a** would be competitively formed *via* the same intermediate **5**, path D is more favorable. Likewise, the formation of **6a** by decomposition of **4** would be readily explained by closure of **5**, which would be generated by the elimination of **2a** from **4**.

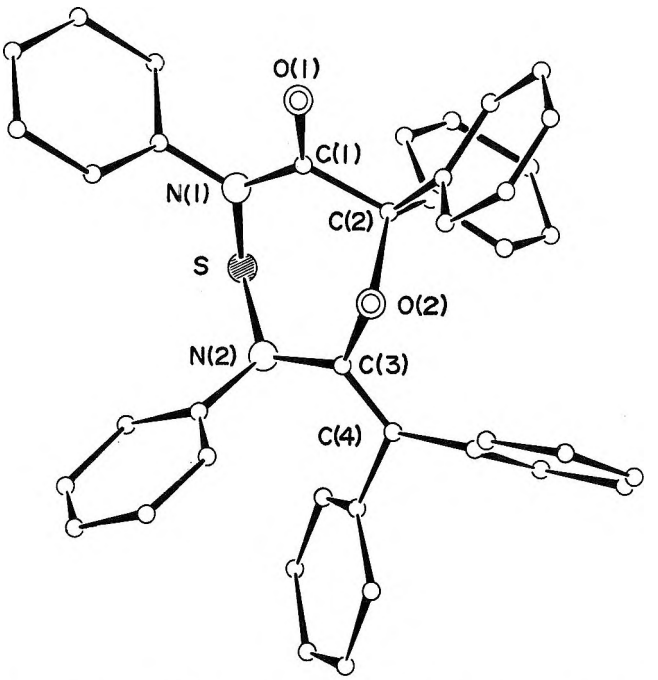
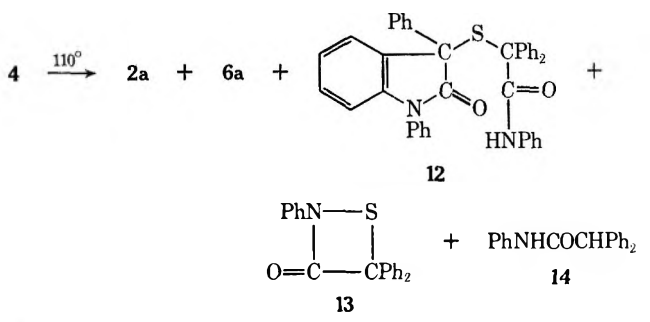
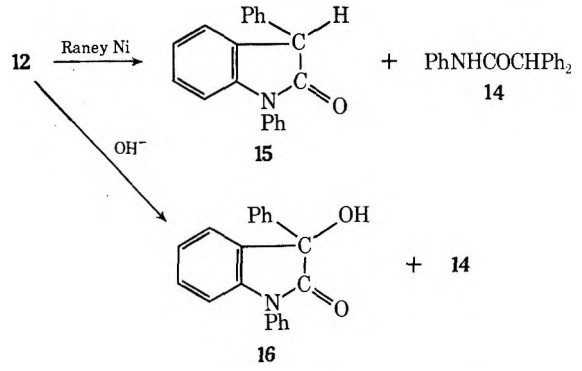



Figure 1.—X-Ray crystal structure of 2,3,4,6,7-pentahydro-2,4,4,7-tetraphenyl-3-oxo-1,5,2,7-thiaoxadiazepin-6-ylidenediphenylmethane (4).

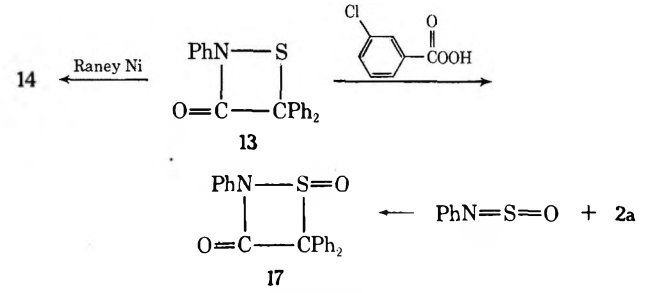
**Thermal Decomposition of Thiaoxadiazepine 4.**—The thiaoxadiazepine derivative **4** on heating at 110° under reduced pressure decomposed to 2,3-dihydro-1,3-diphenyl-2-oxoindol-3-yl diphenyl(phenylcarbamoyl)methyl sulfide (**12**), 2,4,4-triphenyl-1,2-thiazetidin-3-one (**13**), and **6a**, all in 16–24% yield, and small amounts of diphenylacetanilide (**14**) and **2a**.



The reductive desulfurization of **12** by Raney Ni afforded 1,3-diphenyloxindole (**15**) and **14** in excellent yields. On basic hydrolysis, 1,3-diphenyldioxindole (**16**) and **14** were formed in 94 and 74% yields, respectively. On the basis of this chemical evidence, the structure of **12** was assigned as 2,3-dihydro-1,3-diphenyl-2-oxoindol-3-yl diphenyl(phenylcarbamoyl)-methyl sulfide. The structure was confirmed by X-ray crystallographic analysis.[5]



The structure of **13** was determined as follows. The ir spectrum of **13** contains a strong carbonyl absorption at 1710 $cm^{-1}$, while **6a** has the corresponding absorption at 1670 $cm^{-1}$. This indicates that **13** has a ring smaller than **6a**. Reduction of **13** by Raney Ni gave **14** in good yield. Oxidation of **11** by *m*-chloroperbenzoic acid led to 2,4,4-triphenyl-1,2-thiazetidin-3-one 1-oxide (**17**), which was identical by melting point and ir spectrum with an authentic sample,[6] previously prepared from thionylaniline and diphenylketene (**2a**). These chemical properties and physical data are consistent with the structure **13**.



The thermal decomposition of **4** is too complicated to suggest the mechanism of the formation of oxindole **12**, which might be derived from **13** and α-lactam[7] formed by the elimination of **13** from **4**.

(5) Y. Kai, N. Yasuoka, N. Kasai, T. Minami, K. Yamataka, Y. Ohshiro, and T. Agawa, *Chem. Commun.*, 1532 (1971).

(6) H. Beecken and F. Korte, *Tetrahedron*, **18**, 1527 (1962).

(7) It is well known that 1,3,3-triphenylaziridinone gives 1,3-diphenyloxindole: J. C. Sheehan and J. W. Frankenfeld, *J. Amer. Chem. Soc.*, **83**, 4792 (1961).

**Reaction of Di-*tert*-butylsulfur Diimide with Diphenylketene.**—In contrast to **1a**, the reaction of di-*tert*-butylsulfur diimide (**1b**) with **2a** at 0° in ether afforded the 1,2 cycloadduct, 4,4-diphenyl-1-*tert*-butylimino-2-*tert*-butyl-1,2-thiazetidin-3-one (**3b**) in 74% yield. The product **3b**, when refluxed in hexane for 3 hr, was transformed quantitatively into the 1,3 cycloadduct, 4,4-diphenyl-2,5-di-*tert*-butyl-1,2,5-thiadiazolidin-3-one (**6b**). This observation is in agreement with Kresze's[4] result.

The structures of cycloadducts **3b** and **6b** were determined as follows. Cycloadduct **3b** has a strong ir band characteristic of the carbonyl group at 1720 $cm^{-1}$ and two singlet *tert*-butyl signals at 1.15 and 1.53 ppm in the nmr spectrum, which were attributable to imino-*tert*-butyl and amino-*tert*-butyl protons, respectively. On the other hand, cycloadduct **6b** contains a carbonyl absorption at 1655 $cm^{-1}$ in the ir spectrum and two singlet *tert*-butyl protons at 0.95 and 1.42 ppm due to two *tert*-butyls on N-5 and N-2 in the nmr spectrum, respectively.

Furthermore, the structures were clearly decided by hydrogenolysis of the products with Raney Ni. Hydrogenation of **3b** proceeded smoothly to afford *N*-*tert*-butyl-1,1-diphenylacetamide (**18**) in almost quantitative yield, while similar treatment of **6b** gave a mixture of **18** (28%) and *N*-*tert*-butyl-1-*tert*-butylamino-1,1-diphenylacetamide (**19**) (65%). Oxidation of **6b** with hydrogen peroxide gave the product **11b** (78%).

Thus, diphenylsulfur diimide showed different behavior from di-*tert*-butylsulfur diimide in the reaction with diphenylketene. The S=N bond in **3a** and **3b** can be considered to contain the "ylide property" as known in iminosulfurane.[8] Positive charge on the sulfur atom in **3a** would be greater than in **3b**, since the phenyl group can delocalize negative charge on the adjacent nitrogen by resonance. Accordingly, ring opening to the acyclic adduct **5a**, followed by the interception by a second molecule of **2a**, would be easier in **3a**.

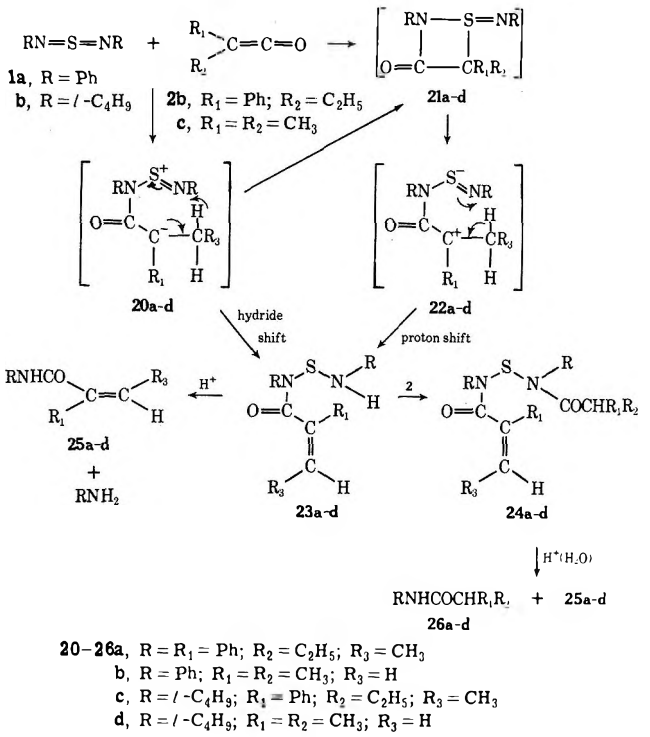
In conclusion, the difference of reactivities between **3a** and **3b** presumably dominates the reaction path.

## Part B

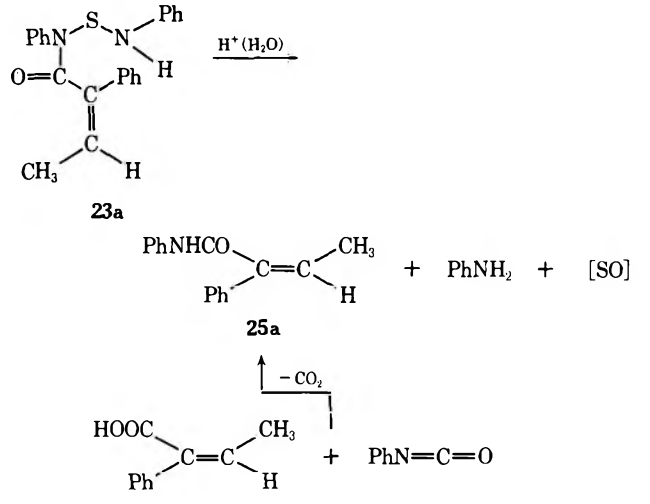
**Reaction of Sulfur Diimides with Phenylethylketene.**—The reaction of diphenylsulfur diimide (**1a**) with phenylethylketene (**2b**) at 0° gave a mixture of *N*,*N*′-diphenyl-*N*-(2-phenyl-*cis*-2-butenoyl)thiobisamine (**23a**) (17%) and its decomposition product, 2-phenyl-*cis*-2-butenoanilide (**25a**) (78%) (Scheme III). In the reaction of di-*tert*-sulfur diimide (**1b**) with **2b** under the same condition, the corresponding product *N*,*N*′-di-*tert*-butyl-*N*-(2-phenyl-*cis*-2-butenoyl)thiobisamine (**23c**) was isolated in 75% yield. Structural assignment to the product **23a** rests upon the following spectroscopic and chemical evidence. The ir spectrum shows the characteristic absorption bands at 3260, 1640, and 1630 $cm^{-1}$ due to NH, amide carbonyl, and C=C bonds, respectively. The nmr spectrum ($CDCl_3$) indicates methyl (d, 3 H), vinyl and NH (m, 2 H), and phenyl protons (m, 15 H) at 1.80, 5.50–6.20, and 6.50–7.55 ppm. Acid-catalyzed hydrolysis led to 2-phenyl-

(8) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 356.

SCHEME III



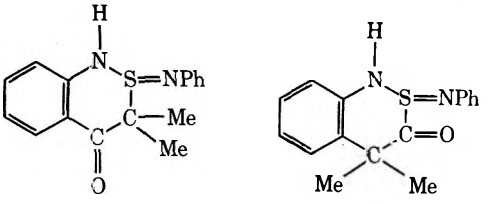
*cis*-2-butenoanilide (**25a**), which was confirmed by comparison of melting point, nmr, and ir with an authentic sample prepared from 2-phenyl-*cis*-2-butenoic acid, phenyl isocyanate, and aniline. Spectroscopic



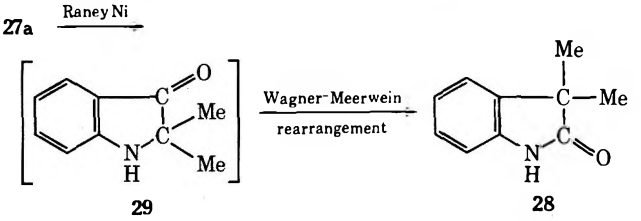
analysis and the chemical evidence, therefore, were consistent with *N*,*N*′-diphenyl-*N*-(2-phenyl-*cis*-2-butenoyl)thiobisamine (**23a**). Assignment of structure **23c** was similarly made.

Thus, no cycloadduct was obtained in the reaction of sulfur diimides with phenylethylketene (**2b**) in place of diphenylketene (**2a**). This result suggests that the thiobisamine derivative was formed either *via* an acyclic dipolar intermediate **20** followed by hydride shift or *via* an alternative dipolar intermediate **22**, followed by proton shift. However, we have no evidence to decide which path is more reasonable.

**Reaction of Sulfur Diimides with Dimethylketene.**—The reaction of **1a** with dimethylketene (**2c**) afforded a 1:1 adduct **27** (18%), *N*,*N*′-diphenyl-*N*-(2-methylpropenoyl)-*N*′-isobutanoylthiobisamine (**24b**) (3%), 2-methylacrylanilide (**25b**) (35%), and isobutyranilide (**26b**) (13%). The ir spectrum of the adduct **27** displayed characteristic bands at 3280 (NH) and 1635 $cm^{-1}$ (carbonyl). The nmr spectrum showed absorptions at 2.00 (two methyls), 6.35 (NH), and 6.48–7.60 ppm (phenyl). There are two possible structures for the adduct **27** consistent with the spectral data: 2-phenylimino-3,3-dimethyl-1*H*-2,1-benzothiazin-4(3*H*)-one (**27a**) and 2-phenylimino-4,4-dimethyl-1*H*-2,1-benzothiazin-3(4*H*)-one (**27b**). Although the nmr spec-



trum is compatible with both structures, the ir spectrum suggests that **27a** is the more probable structure on the basis of the low-frequency position of the carbonyl group. Reductive desulfurization of **27** with Raney Ni afforded 3,3-dimethyloxindole (**28**) (92%), which was identified by comparison of the ir spectrum and melting point with those of an authentic sample.[9] This chemical evidence seems to support the structure **27b**, since the formation of 2,2-dimethylindoxyl (**29**) is

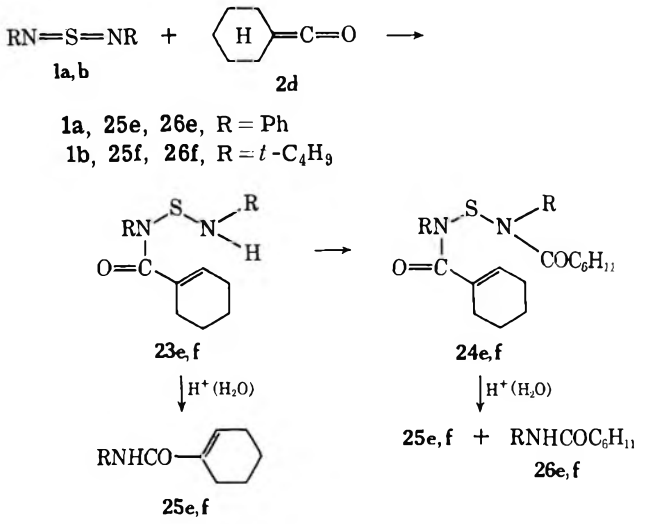


predicted from **27a**. However, it is well known that 2,2-disubstituted indoxyl is readily rearranged to 3,3-disubstituted oxindole.[10] Accordingly, it is reasonable to consider that the product **29**, which would be yielded by reduction of **27a**, underwent a Wagner–Meerwein rearrangement to lead to **28** under the experimental condition. On the basis of such spectral and chemical evidence, the 1:1 adduct was assigned the structure 2-phenylimino-3,3-dimethyl-1*H*-2,1-benzothiazin-4(3*H*)-one (**27a**).

In the reaction between **1b** and **2c**, no thiobisamine derivative (**23d** and/or **24d**) was obtained but *N*-*tert*-butyl-2-methylacrylamide (**25d**) and *N*-*tert*-butylisobutyramide (**26d**) were isolated in 69 and 9% yields, respectively.

**Reaction of Sulfur Diimides with Pentamethyleneketene.**—The reaction between **1a** and pentamethyleneketene (**2d**) yielded *N*,*N*′-diphenyl-*N*-(1-cyclohexenoyl)-*N*′-cyclohexanoylthiobisamine (**24e**) (55%), which would be provided by the addition of **2d** to *N*,*N*′-diphenyl-*N*-(1-cyclohexenoyl)thiobisamine (**23e**) initially formed, together with 1-cyclohexenoanilide (**25e**) (21%) and hexahydrobenzoanilide (**26e**) (5%). The difference in the yields between **25e** and **26e** evidently indicates the formation of **23e**, which might not be isolated for its instability, since only **25e** from **23e** and an

(9) K. Brunner, *Monatsh.*, **18**, 98 (1897).
(10) B. Witkop and A. Ek, *J. Amer. Chem. Soc.*, **73**, 5664 (1951).

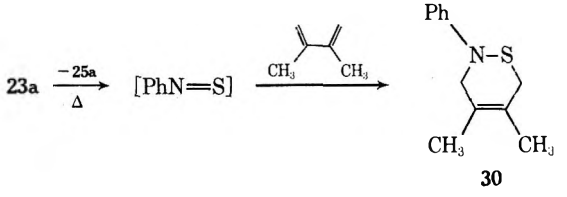



equimolar amount of **25e** and **26e** from **24e** should be obtained.

In the reaction using **1b**, no thiobisamine derivative (**23f** and/or **24f**) was isolated, but its decomposition product, *N-tert*-butyl-1-cyclohexenylcarboxamide (**25f**), was obtained in 87% yield.

**Reaction of Thiobisamine 23a with 2,3-Dimethylbutadiene.**—Treatment of **23a** with 2,3-dimethylbutadiene at 140° in a sealed tube gave 2-phenyl-4,5-dimethyl-3,6-dihydro-1,2-thiazine (**30**) (35%) and **25a** (80%).

The formation of the thiazine derivative **30** suggests




similarly the presence of thioaniline as a dienophile, as proposed by Tavs.[11] In the reaction using tetraphenylcyclopentadienone in place of 2,3-dimethylbutadiene, no 1,2-thiazine derivative was formed but azobenzene was obtained in 65% yield.

In conclusion, ketenes containing hydrogen on the $\alpha$ carbon atom react with sulfur diimide to give thiobisamine derivatives, regardless of the substituents on the sulfur diimide.

## Experimental Section

**General.**—All melting points of products obtained (Table I) were determined with a Yanagimoto micro melting apparatus and uncorrected. The nmr spectra were obtained on a Joellmm 3H-60 spectrometer with tetramethylsilane as an internal standard. The ir spectra were recorded with a Jasco-IR-E spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

**Materials.**—Diphenylsulfur diimide[12] and di-*tert*-butylsulfur diimide[13] were prepared according to the established procedures.

Phenylethylketene was synthesized from 2-phenylbutanoyl chloride and triethylamine, bp 48° (2 mm), ir (neat) 2300 cm$^{-1}$ (C=C=O).

**2,3,4,6,7-Pentahydro-2,4,4,7-tetraphenyl-3-oxo-1,5,2,7-thiaoxadiazepin-6-ylidenediphenylmethane** (4).—Diphenylsulfur diimide (**1a**) (2.14 g, 0.01 mol) dissolved in 50 ml of benzene was added dropwise to a stirred solution of diphenylketene (2a) (3.88 g, 0.02 mol) in 50 ml of benzene at 6–8° under an atmosphere of nitrogen. After stirring for 0.5 hr, the solution was allowed to warm to ambient temperature and stirring was continued for 0.5 hr. Benzene was then removed under reduced pressure. The residue immediately crystallized to give 4.5 g (75%) of **4**, which was washed with anhydrous ether to afford pure **4**: mp 101–110° dec; ir (Nujol) 1685 (C=O), 1625 (C=C), and 1275 cm$^{-1}$ (COC); nmr ($CDCl_3$) $\delta$ 6.60–7.60 (m, phenyl protons); mass spectrum (70 eV) no molecular ion, *m/e* 408 ($M^+ - Ph_2CCO$), 317 ($M^+ - Ph_2CCONPh$), 285 ($Ph_2CCOPh^+$), 256 ($PhNCPh_2^+$).

*Anal.* Calcd for $C_{40}H_{30}N_2O_2S$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.69; H, 5.08; N, 4.60.

In the reaction using an equimolar amount of **1a** to **2a** under the same condition, **4** was obtained in 32% yield together with unreacted **1a** (24%).

**2,4,4,5-Tetraphenyl-1,2,5-thiadiazolidin-3-one** (**6a**). **Procedure A.**—A mixture of 4.81 g (8 mmol) of **4** and 1.48 g (6.9 mmol) of **1a** in 50 ml of benzene was refluxed for 3 hr. The solvent was removed *in vacuo* and the resulting solid residue was recrystallized from benzene–ethanol to give 4.60 g (76%) of **6a**: mp 167° (lit.[2] mp 167°); ir (Nujol) 1670 cm$^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 6.75–7.75 (m, phenyl protons); mass spectrum (70 eV) *m/e* 408 ($M^+$), 288 ($M^+ - PhNHCO$), 257 ($M^+ - PhNCO - S$), 214 ($PhNSNPh^+$), and 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{26}H_{20}N_2OS$: C, 76.45; H, 4.94; N, 6.86. Found: C, 76.29; H, 4.99; N, 6.80.

**Procedure B.**—A solution of 3.70 g (0.0173 mol) of **1a** in 50 ml of benzene was added dropwise to a solution of 3.9 g (0.02 mol) of **2a** in 50 ml of benzene at ambient temperature under a nitrogen atmosphere. After stirring at ambient temperature for 0.5 hr, the solution was refluxed for 3 hr. After work-up similar to above, **6a** was obtained in a yield of 4.70 g (67%).

**Ethanolysis of 4.**—A solution of 2.0 g (3.32 mmol) of **4** in 50 ml of 99% ethanol was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was recrystallized from benzene–ethanol to afford 0.60 g (44%) of **6a**. The filtrate was chromatographed on neutral alumina using benzene as eluent. The first fraction was concentrated and the residue was recrystallized from benzene–hexane to give 0.30 g (38%) of **diphenylacetic acid ethyl ester** (**9**), mp 56–58° (lit.[14] mp 57–58°). Similar treatment of the second fraction gave 0.30 g (27%) of **1-ethoxy-1,1-diphenylacetanilide** (**10**), mp 134° (lit.[1] mp 133.5–134.5°). Similar treatment of the third fraction afforded 0.15 g (11%) of **2,4,4,5-tetraphenyl-1,2,5-thiadiazolidin-3-one 1-oxide** (**11a**): mp 179–180.5° (hexane–benzene); ir (Nujol) 1720 (C=O) and 1160 cm$^{-1}$ (S=O); nmr ($CDCl_3$) $\delta$ 6.80–8.00 (m, phenyl protons); mass spectrum (70 eV) *m/e* 424 ($M^+$), 305 ($M^+ - PhNCO$), 257 ($M^+ - PhNCO - SO$), and 180 ($Ph_2CN^+$).

TABLE I
SOME PHYSICAL DATA OF THE REACTION PRODUCTS OF SULFUR DIIMIDES WITH DIPHENYLKETENE AND THEIR DECOMPOSITION PRODUCTS

| Product | Ir (Nujol), cm$^{-1}$ | Nmr ($CDCl_3$), $\delta$ ppm | Mp, °C |
|---|---|---|---|
| **6a** | 1670 | 6.75–7.75 (m, phenyl protons) | 167 |
| **4** | 1685 | 6.60–7.60 (m, phenyl protons) | 101–110 dec |
| **11a** | 1720 | 6.80–8.80 (m, phenyl protons) | 179–180.5 |
| **13** | 1710 | 6.95–7.60 (m, phenyl protons) | 156–158 |
| **17** | 1740 | 7.80–7.83 (m, phenyl protons) | 117–118 (lit.[6] 116–117.5) |
| **3b** | 1720 | 1.15 (s, 9 H, S=N-*t*-Bu) 1.53 (s, 9 H, >N-*t*-Bu) | 96–98 dec |
| **6b** | 1655 | 0.95 (s, 9 H, >N-*t*-Bu) 1.42 (s, 9 H, CON-*t*-Bu) | 103–104.5 |
| **11b** | 1705 | 1.17 (s, 9 H, >N-*t*-Bu) 1.58 (s, 9 H, CON-*t*-Bu) | 180–181 |

(11) P. Tavs, *Angew. Chem.*, **78**, 1057 (1966).
(12) T. Minami, H. Miki, H. Matsumoto, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, 3049 (1968).
(13) R. Appel and J. Kohnke, *Chem. Ber.*, **103**, 2152 (1970).
(14) R. Symons and T. Zincke, *Justus Liebigs Ann. Chem.*, **171**, 129 (1874).

*Anal.* Calcd for $C_{26}H_{20}N_2O_2S$: C, 73.64; H, 4.67; N, 6.68. Found: C, 73.57; H, 4.75; N, 6.60.

**11a from 6a and Hydrogen Peroxide.**—A mixture of **6a** (2.40 g, 5 mmol) and 35% concentrated hydrogen peroxide (1 ml) in 50 ml of tetrahydrofuran was allowed to stir at 0° for 1.5 hr. After removal of solvent *in vacuo*, the resulting residue was extracted with benzene, followed by washing with water, drying over sodium sulfate, and evaporation of benzene. The residue was recrystallized from hexane–benzene to give **11a** (1.52 g, 36%).

**Pyrolysis of 4.**—The compound **4** (5.60 g, 9.3 mmol) was pyrolyzed at 110° under reduced pressure (1 mm) for 0.5 hr. The distillate (trace) was identified as diphenylketene. The residue was triturated with ether (10 ml) and then filtration gave the mixture of **2,3-dihydro-1,3-diphenyl-2-oxoindol-3-yl diphenyl(phenylcarbamoyl)methyl sulfide** (**12**) (1.24 g, 22%), **2,4,4-triphenyl-1,2-thiazetidin-3-one** (**13**) (0.70 g, 24%), and **6a** (0.28 g), which was separated by recrystallization from benzene–hexane. The crude compound **12** was recrystallized from benzene–ethanol, giving a pure sample, mp 208–209°, as a white, granular crystal: ir (Nujol) 3280, 3200 (NH), 1700 (indole ring C=O), 1690 (amide C=O), and 1550 $cm^{-1}$ (NH); nmr ($CDCl_3$) $\delta$ 6.60–7.75 (m, 29 H, phenyl protons) and 9.82 (broad, 1 H, amide proton); mass spectrum (70 eV) *m/e* 602 ($M^+$), 317 ($M^+ - PhNCOCPh_2$), 285 ($M^+ - PhNCOCPh_2 - S$), and 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{40}H_{30}N_2O_2S$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.91; H, 4.91; N, 4.60.

The crude product **13** was recrystallized from benzene–hexane, giving a pure sample, mp 156–158°, as pale yellow plates: ir (Nujol) 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 6.95–7.60 (m, phenyl protons); mass spectrum (70 eV) *m/e* 317 ($M^+$), 285 ($M^+ - S$), 256 ($M^+ - S - CO - H$), and 198 ($Ph_2CS^+$).

*Anal.* Calcd for $C_{20}H_{15}NOS$: C, 75.69; H, 4.67; N, 4.41. Found: C, 75.75; H, 4.68; N, 4.40.

The filtrate was chromatographed over neutral alumina using hexane, benzene, and ethanol as eluent to give **6a** (0.32 g) and **diphenylacetanilide** (**14**) (0.20 g, 8%), mp 184–185° (lit.[15] mp 180°). The combined yield of **6a** was 0.60 g (16%).

**Oxidation of 13.**—A solution of 0.70 g (2.23 mmol) of **13** and 1.0 g of *m*-chloroperbenzoic acid in 50 ml of chloroform was allowed to stir at room temperature for 24 hr. The solution was washed with 50 ml of 10% aqueous sodium sulfite, followed by washing with 50 ml of 5% aqueous sodium bicarbonate and 3 × 50 ml of water, and dried over sodium sulfate. After removal of solvent *in vacuo*, the residue was recrystallized from ether–benzene (9:1) to give 0.02 g (27%) of pure **2,4,4-triphenyl-1,2-thiazetidin-3-one 1-oxide** (**17**): mp 117–118° (lit.[6] mp 116–117.5°); ir (Nujol) 1740 (C=O), 1126 (S=O), and 1141 $cm^{-1}$ (S=O); nmr ($CDCl_3$) $\delta$ 7.08–7.83 (m, phenyl protons); mass spectrum (70 eV) no molecular ion, *m/e* 285 ($M^+ - SO$), 256 ($M^+ - 1 - SO - CO$), and 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{20}H_{15}NO_2S$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.07; H, 4.54; N, 4.26.

The filtrate was chromatographed on neutral alumina. Elution with benzene–ethanol gave 0.25 g (41%) of **14**.

**Reduction of 13.**—A solution of 0.50 g (1.58 mmol) of **13** in 50 ml of tetrahydrofuran containing 1 g of Raney Ni was allowed to stir under reflux for 5 hr. The organic layer was separated and concentrated. Recrystallization of the residue from benzene gave 0.37 g (82%) of **14**.

**Reduction of 12.**—Reduction of **12** (1.70 g, 2.8 mmol) with Raney Ni (2 g) in tetrahydrofuran (50 ml) was similarly carried out. After removal of solvent *in vacuo*, the residue was chromatographed on alumina to give 1.10 g (92%) of **14** and 1.00 g (85%) of **1,3-diphenyloxindole** (**15**): mp 114–115° (lit.[7] mp 113–114°); ir (Nujol) 1720 (C=O) and 1610 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 4.77 (broad, 1 H, >CHPh) and 6.55–7.65 (m, 14 H, phenyl protons); mass spectrum (70 eV) *m/e* 285 ($M^+$) and 256 ($M^+ - 1 - CO$).

*Anal.* Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.36; N, 4.91. Found: C, 84.12; H, 5.57; N, 4.82.

**Base-Catalyzed Hydrolysis of 12.**—A solution of **12** (1.70 g, 2.8 mmol) in tetrahydrofuran (100 ml) was refluxed with aqueous sodium hydroxide (10 ml, 20%) for 20 hr. After removal of solvent, the residue was extracted with benzene, followed by washing with water and drying over sodium sulfate. The benzene layer gave 0.60 g (74%) of **14**. The water layer was neutralized with hydrochloric acid and extracted with benzene. The benzene extract afforded 0.80 g (94%) of **1,3-diphenyldioxindole** (**16**): mp 172–173°; ir (Nujol) 3420 (OH), 1710 (C=O), and 1175 $cm^{-1}$ (CO); nmr ($CDCl_3$) $\delta$ 4.13 (s, 1 H, OH) and 6.72–7.62 (m, 14 H, phenyl protons); mass spectrum (70 eV)-*m/e* 301 ($M^+$), 285 ($M^+ - O$), 272 ($M^+ - 1 - CO$), and 256 ($M^+ - CO - OH$).

*Anal.* Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.73; H, 4.80; N, 4.57.

**4,4-Diphenyl-1-*tert*-butylimino-2-*tert*-butyl-1,2-thiazetidin-3-one** (**3b**).—A solution of di-*tert*-butylsulfur diimide (**1b**) (3.0 g, 0.02 mol) in 30 ml of ether was added dropwise to a stirred solution of **2a** (3.88 g, 0.02 mol) in 30 ml of ether at 0–2° under a nitrogen atmosphere. After stirring for 0.5 hr, the solvent was removed *in vacuo* at room temperature. The residue was crystallized from cold hexane, and standing at −20° gave 5.42 g (74%) of **3b**: mp 96–98° dec; ir (Nujol) 1720 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.15 (s, 9 H, >S=N-*t*-Bu), 1.53 (s, 9 H, CON-*t*-Bu), and 7.02–7.55 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 368 ($M^+$), 312 ($M^+ + 1 - t$-Bu), 256 [$M^+ + 2 - 2(t$-Bu)], 213 ($Ph_2CHNS^+$), 194 ($Ph_2CCO^+$), and 180 ($Ph_2CN^+$).

*Anal.* Calcd for $C_{22}H_{28}N_2OS$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.99; H, 7.59; N, 7.64.

**4,4-Diphenyl-2,5-di-*tert*-butyl-1,2,5-thiadiazolidin-3-one** (**6b**).—A solution of 0.48 g (1.34 mmol) of **3b** in 50 ml of hexane was allowed to reflux for 4 hr. The solution was concentrated to one fifth of its original volume and allowed to stand at −20° to give 0.46 g (96%) of **6b**: mp 103–104.5°; ir (Nujol) 1655 $cm^{-1}$ (CO); nmr ($CDCl_3$) $\delta$ 0.95 (s, 9 H, >N-*t*-Bu), 1.42 (s, 9 H, CON-*t*-Bu) and 7.03–7.68 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 368 ($M^+$), 312 ($M^+ + 1 - t$-Bu), 256 [$M^+ + 2 - 2(t$-Bu)], 213 ($Ph_2CHNS^+$), 194 ($Ph_2CCO^+$), and 180 ($Ph_2CN^+$).

*Anal.* Calcd for $C_{22}H_{28}N_2OS$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.40; H, 7.65; N, 7.57.

**Reduction of 3b.**—**3b** (0.45 g, 1.22 mmol) with Raney Ni (1 g) in THF was hydrogenated at room temperature for 3 hr in the same manner as **13**. After similar treatment, *N-tert*-butyl-1,1-diphenylacetamide (**18**) was obtained in a yield of 0.3 g (92%): mp 182–189° subl (lit.[16] mp 201–202°); ir (Nujol) 3300 (NH), 1635 (C=O), and 1550 $cm^{-1}$ (NH); nmr ($CDCl_3$) $\delta$ 1.30 (s, 9 H, *t*-Bu), 4.82 (s, 1 H, –CH<), 5.47 (broad, 1 H, NH), and 3.07–3.53 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 267 ($M^+$).

*Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.49; H, 7.86; N, 5.30.

**Reduction of 6b.**—A mixture of **6b** (1.0 g, 2.7 mmol) and Raney Ni (1 g) in 50 ml of ethanol was heated at reflux for 6 hr. After similar work-up the residue was crystallized from benzene–hexane to give 0.02 g (28%) of **18**.

The filtrate was evaporated and the residue was crystallized from hexane to give 0.59 g (65%) of ***N-tert*-butyl-1-*tert*-butylamino-1,1-diphenylacetamide** (**19**): mp 132–133.5°; ir (Nujol) 3320 (NH) and 1660 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 0.90 (s, 9 H, >N-*t*-Bu), 1.20 (s, 9 H, CON-*t*-Bu), 1.90 (broad, 1 H, amine proton), 7.02–7.35 [m, 6 H, amide proton (1 H) and phenyl protons (5 H)], and 7.35–7.77 (m, 5 H, phenyl protons); mass spectrum (70 eV) *m/e* 338 ($M^+$).

*Anal.* Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.14; H, 9.15; N, 8.29.

**4,4-Diphenyl-2,5-di-*tert*-butyl-1,2,5-thiadiazolidin-3-one 1-Oxide** (**11b**).—This derivative was prepared in the same way as **11a**, from the oxidation of 4.05 g (0.011 mol) of **6b** with 35% concentrated hydrogen peroxide (2 ml). The yield of **11b** was 3.30 g (78%) (after recrystallization from benzene–hexane): mp 180–181°; ir (Nujol) 1705 (C=O) and 1120 $cm^{-1}$ (S=O); nmr ($CDCl_3$) $\delta$ 1.15 (s, 9 H, >N-*t*-Bu), 1.57 (s, 9 H, CON-*t*-Bu), and 7.15–7.85 (m, 10 H, phenyl protons); mass spectrum (70 eV) *m/e* 384 ($M^+$), 313 ($M^+ - t$-BuN), and 285 ($M^+ - t$-BuNCO).

*Anal.* Calcd for $C_{22}H_{28}N_2O_2S$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.45; H, 7.32; N, 6.97.

**Reaction between Diphenylsulfur Diimide** (**1a**) **and Phenylethylketene** (**2b**).—The reaction between **1a** (1.73 g, 8.08 mmol) and phenylethylketene (**2b**) (2.20 g, 15 mmol) was carried out in a similar manner as previously described for the reaction of **1b** with **2a**. The ethereal solution was concentrated *in vacuo* to one-third of its original volume and allowed to stand at 0° overnight. Filtration gave 0.50 g (17%) of *N,N'*-**diphenyl-*N*-(2-phenyl-*cis*-**

(15) H. Staudinger, *Chem. Ber.*, **38**, 1735 (1905).

(16) J. J. Ritter and F. X. Murphy, *J. Amer. Chem. Soc.*, **74**, 763 (1952).

**2-butenoyl)thiobisamine (23a).** The thiobisamine derivative **23a** was recrystallized from ether: mp 123–124.5°; ir (Nujol) 3260 (NH), 1640 (C=O), and 1630 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 1.80 (d, $J$ = 6.7 Hz, 3 H, $=CHCH_3$), 5.50–6.20 (m, 2 H, $=CHCH_3$ and NH), and 6.50–7.55 (m, 15 H, phenyl protons); mass spectrum (70 eV) $m/e$ 360 ($M^+$), 237 ($M^+$ − PhNS), 145 ($M^+$ − PhNSNHPh), and 117 ($M^+$ − PhCONSNHPh).

*Anal.* Calcd for $C_{22}H_{20}N_2OS$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.39; H, 5.72; N, 7.69.

The filtrate was chromatographed on alumina using benzene–ethanol (95:5) as eluent to give **2-phenyl-*cis*-2-butenoanilide (25a)** (1.5 g, 78%). Recrystallization from benzene–hexene afforded the analytical sample: mp 154–155°; ir (Nujol) 3280 (NH), 1650 (C=O), 1630 (C=C), and 1550 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.97 (d, $J$ = 7.2 Hz, 3 H, $=CHCH_3$), 6.13 (d, $J$ = 7.2 Hz, 1 H, $=CHCH_3$), and 7.00–7.85 (m, 11 H, phenyl protons and NH); mass spectrum (70 eV) $m/e$ 237 ($M^+$), 145 ($M^+$ − PhNH), and 117 ($M^+$ − PhNHCO).

*Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.21; H, 6.22; N, 6.02.

**Preparation of Authentic 2-Phenyl-*cis*-2-butenoanilide.**—A mixture of 2-phenyl-*cis*-2-butenoic acid[17] (2.0 g, 0.0123 mol), phenyl isocyanate (1.50 g, 0.0126 mol), and triethyamine (2 ml) in 50 ml of toluene was refluxed for 10 hr. The solvent was removed under reduced pressure and the residue was crystallized from benzene–hexane to give 1.90 g (65%) of **2-phenyl-*cis*-2-butenoanilide**, mp 154°, which was consistent with **25a** obtained in the above experiment.

**Acid-Catalyzed Hydrolysis of 23a.**—A solution of **23a** (2.0 g, 5.56 mmol) in THF (50 ml) containing 48% aqueous HBr (4 ml) was refluxed for 5 hr. After removal of solvent, the residue was extracted with benzene, followed by washing with water and drying over sodium sulfate. The benzene layer gave 1.0 g (76%) of **25a**.

**Reaction between Diphenylsulfur Diimide (1a) and Pentamethyleneketene (2d).**—Hexahydrobenzoic acid chloride (7.35 g, 0.05 mol) in 50 ml of benzene was added dropwise to a stirred solution containing triethylamine (6.06 g, 0.06 mol) and diphenylsulfur diimide (3.57 g, 0.0167 mol) in 50 ml of benzene at room temperature under a nitrogen atmosphere. After the solution was stirred for 20 hr, the resulting amine salt was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was crystallized from benzene to give 4.0 g (55%) of **$N,N'$-diphenyl-$N$-(1-cyclohexenoyl)-$N'$-cyclohexanoylthiobisamine (24e)**: mp 195–196°; ir (Nujol) 1690 (C=O), 1680 (C=O), and 1645 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 0.72–2.12 (m, 18 H), 2.63 (broad, 1 H, cyclohexanoyl 1-proton), 5.60 (broad, 1 H, olefinic proton), and 6.95–7.55 (m, 10 H, phenyl protons); mass spectrum (70 eV) $m/e$ 434 ($M^+$), 324 ($M^+ + 1 - C_6H_{11}CO$), 231 ($M^+ + 1 - C_6H_{11}CONPh$), 201 ($C_6H_{11}CONPh - 1)^+$, 123 ($PhNS^+$), and 110 ($C_6H_{11}CO + 1)^+$.

*Anal.* Calcd for $C_{26}H_{30}N_2O_2S$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.54; H, 6.85; N, 6.31.

The filtrate was chromatographed on neutral alumina using benzene–hexane as eluent to give a mixture of **1-cyclohexenoanilide (25e)** (0.72 g, 21%) and **hexahydrobenzoanilide (26e)** (0.18 g, 5%), whose ratio was determined with its nmr spectrum. The mixture was recrystallized from benzene–hexane to give pure **25e**: mp 125–127°; ir (Nujol) 3280 (NH), 1650 (C=O), 1625 (C=C), and 1540 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.05–2.55 (m, 8 H), 6.65 (broad, 1 H, olefinic proton), 6.85–7.80 (m, 5 H, phenyl protons), and 7.90 (broad, 1 H, NH); mass spectrum (70 eV) $m/e$ 201 ($M^+$) and 109 ($M^+$ − PhNH).

*Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.31; H, 7.80; N, 7.02.

The filtrate was concentrated and the residue was recrystallized from benzene–hexane to give pure **26e**: mp 137–138° (lit.[18] mp 130–131°); ir (Nujol) 3260 (NH), 1655 (C=O), and 1545 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 0.90–2.50 (m, 11 H), 6.85–7.65 (m, 5 H, phenyl protons), and 7.80 (broad, 1 H, amide proton); mass spectrum (70 eV) $m/e$ 203 ($M^+$).

*Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.78; H, 8.43; N, 6.89. Found: C, 76.94; H, 8.48; N, 6.94.

**Acid-Catalyzed Hydrolysis of 24e.**—A solution of **24e** (2.0 g, 4.61 mmol) in THF was treated under the same condition as **23a**. After similar work-up, a mixture of **25e** (0.52 g, 93%) and **26e** (0.50 g, 91%), whose ratio was determined with the nmr spectrum, was given.

**Reaction between Diphenylsulfur Diimide (1a) and Dimethylketene (2c).**—The reaction was carried out at 6–8° for 1 hr using the procedure described above with isobutyric acid chloride (21.3 g, 0.20 mol), triethylamine (24.2 g, 0.24 mol), and **1a** (20 g, 0.0805 mol) in dry benzene. After removal of amine salt by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was crystallized from benzene to afford a mixture of **2-phenylimino-3,3-dimethyl-1*H*-2,1-benzothiazin-4-(3*H*)-one (27a)** and **$N,N'$-diphenyl-$N$-(2-methylpropenoyl)-$N'$-isobutanoylthiobisamine (24b)**. Pure samples of individual **27a** (4.2 g, 18%) and **24b** (0.8 g, 3%) were isolated by repeated recrystallization of the mixture from benzene.

**27a** had mp 173–175°; ir (Nujol) 3280 (NH) and 1635 $cm^{-1}$ (CO); nmr ($CDCl_3$) δ 2.00 (broad, 6 H, $>C(CH_3)_2$), 6.35 (broad, 1 H, NH), and 6.48–7.60 (m, 9 H, phenyl protons); mass spectrum (70 eV) $m/e$ 284 ($M^+$), 161 ($M^+$ − PhNS), 146 ($M^+$ − PhNSNH), and 123 ($PhNS^+$).

*Anal.* Calcd for $C_{16}H_{16}N_2OS$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.71; H, 5.79; N, 9.69.

**24b** had mp 183–185.5°; ir (Nujol) 1695 (CO), 1675 (CO), and 1630 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 0.87 (d, 6 H, $J$ = 6.3 Hz, $-CH(CH_3)_2$), 1.58 (broad, 3 H, $CH_3C=CH_2$), 3.13 (m, 1 H, $-CH<$), 4.85 [broad, 1 H, COC=CH (*trans*)], 5.03 [broad, 1 H, COC=CH (*cis*)], and 6.98–7.56 (m, 10 H, phenyl protons); mass spectrum (70 eV) $m/e$ 354 ($M^+$), 284 ($M^+$ − $(CH_3)_2CCO$), 191 ($M^+$ − $PhNHCOCHC(CH_3)_2$), 161 ($M^+$ − $PhNSCOC(CH_3)_2$), and 123 ($PhNS^+$).

*Anal.* Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.00; N, 7.72.

The filtrate was chromatographed on alumina using benzene as eluent to afford a mixture of 4.47 g (35%) of **2-methylacrylanilide (25b)** and 1.68 g (13%) of **isobutyranilide (26b)**, whose ratio was determined with its nmr spectrum. Pure samples of individual **25b** and **26b** were isolated by recrystallization of the mixture from benzene–hexane.

**25b** had mp 86–87° (lit.[19] mp 87°); ir (Nujol) 3300 (NH), 1650 (CO), 1615 (C=C), and 1525 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 2.00 (broad, 3 H, $CH_3C=CH_2$), 5.38 (broad, 1 H, $CH_3C=CH$), 5.72 (broad, 1 H, COC=CH), 6.88–7.65 (m, 5 H, phenyl protons), and 8.00 (broad, 1 H, NH); mass spectrum (70 eV) $m/e$ 161 ($M^+$) and 146 ($M^+$ − $CH_3$).

*Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.67. Found: C, 74.64; H, 6.89; N, 8.67.

**26b** had mp 106–108° (lit.[20] mp 105°); ir (Nujol) 3280 (NH), 1655 (CO), and 1545 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.12 (d, 6 H, two methyl protons), 2.55 (m, 1 H, >CH–), 6.75–7.60 (m, 5 H, phenyl protons), and 9.08 (broad, 1 H, NH); mass spectrum (70 eV) $m/e$ 163 ($M^+$).

*Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.78; H, 8.21; N, 8.87.

**Reduction of 27a.**—A solution containing **27a** (2.5 g, 8.8 mmol) and Raney Ni (2 g) in 50 ml of THF was refluxed for 5 hr. The organic layer was separated and concentrated under reduced pressure. The residue was chromatographed on alumina to give 1.30 g (92%) of **3,3-dimethyloxindole (28)**: mp 157–158° (lit.[9] mp 152–153°); ir (Nujol) 3160 (NH), 1715 (C=O), 1675 (C=O), and 1620 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 1.40 (s, 6 H, $>C(CH_3)_2$), 6.85–7.25 (m, 4 H, phenyl protons), and 9.85 (broad, 1 H, NH); mass spectrum (70 eV) $m/e$ 161 ($M^+$) and 146 ($M^+$ − $CH_3$).

*Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.86; H, 6.71; N, 8.80.

**Reaction between Di-*tert*-butylsulfur Diimide (1b) and Phenylethylketene (2b).**—The reaction was carried out at 0° using the procedure described above with **1b** (3.48 g, 0.02 mol) and **2b** (2.92 g, 0.02 mol) in petroleum ether (bp 30–60°). The reaction mixture was concentrated to one fifth of its original volume and allowed to stand at −20° to give 4.8 g (75%) of **$N,N'$-di-*tert*-butyl-$N$-(2-phenyl-*cis*-2-butenoyl)thiobisamine (23c)**: mp 72.5–74°; ir (Nujol) 3320 (NH) and 1635 $cm^{-1}$ (CO); nmr ($CDCl_3$) δ 1.40 (s, 9 H, NH-*t*-Bu), 1.59 (s, 9 H, CON-*t*-Bu), 1.88 (d, $J$ = 6.6 Hz, 3 H, $=CHCH_3$), 3.45 (broad, 1 H, NH), 5.98 (q, $J$ = 6.6 Hz, 1 H, $=CHCH_3$), and 7.18–7.35 (m, 5 H, phenyl protons); mass spectrum (70 eV) $m/e$ 320 ($M^+$), 249 ($M^+$ −

(17) L. A. Carpino, *J. Amer. Chem. Soc.*, **80**, 601 (1958).
(18) W. Scharvin, *Chem. Ber.*, **30**, 2863 (1897).
(19) W. Autenrieth and C. Pretzell, *ibid.*, **36**, 1269 (1903).
(20) W. Crossley and W. H. Perkin, *J. Chem. Soc.*, **73**, 34 (1898).

N-*t*-Bu), 217 ($M^+$ − SN-*t*-Bu), 145 (PhC(CO)=$CHCH_3$)$^+$, and 117 (PhC=$CHCH_3^+$).

*Anal.* Calcd for $C_{18}H_{28}N_2OS$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.47; H, 9.01; N, 8.51.

**Reduction of 23c.**—Reduction of **23c** (1.60 g, 5 mmol) with Raney Ni (1 g) in 50 ml of ethanol was similarly carried out. After removal of solvent, the resulting residue was crystallized from benzene–hexane to give 0.76 g (69%) of *N-tert*-**butyl-2-phenylbutyramide** (**26c**): mp 111.5–112.5°; ir (Nujol) 3320 (NH), 1635 (CO), and 1545 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 0.87 (t, 3 H, $CH_2CH_3$), 1.28 (s, 9 H, *t*-Bu), 1.95 (m, 2 H, $CHCH_2CH_3$), 3.15 (t, 1 H, $CHCH_2$–), 5.35 (broad, 1 H, NHCO), and 7.28 (s, 5 H, phenyl protons); mass spectrum (70 eV) *m/e* 219 ($M^+$) and 120 ($M^+$ − *t*-BuNCO).

*Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.76; H, 9.81; N, 6.19.

The filtrate was concentrated and the crystallization of the residue from hexane afforded 0.21 g (19%) of *N-tert*-**butyl-2-phenyl-*cis*-2-butenoamide** (**25c**): mp 108–109°; ir (Nujol) 3240 (NH), 1640 (CO), 1625 (C=C), and 1545 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu), 1.93 (d, $J$ = 6.6 Hz, 3 H, $=CHCH_3$), 5.51 (broad, 1 H, NH), 6.02 (q, 1 H, $J$ = 6.6 Hz, $=CHCH_3$), and 7.12–7.45 (m, 5 H, phenyl protons); mass spectrum (70 eV) *m/e* 217 ($M^+$), 161 ($M^+$ − *t*-Bu), 145 ($M^+$ − NH-*t*-Bu), and 117 ($M^+$ − *t*-BuNHCO).

*Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.18; H, 9.02; N, 6.48.

**Preparation of Authentic *N-tert*-Butyl-2-phenyl-*cis*-2-butenoamide.**—*tert*-Butylamine (0.34 g, 5 mmol) in 20 ml of benzene was added dropwise to a stirred solution of 2-phenyl-*cis*-2-butenoyl chloride (0.5 g, 2.76 mmol) and triethylamine (0.51 g, 5 mmol) in 20 ml of benzene at room temperature over a period of 0.5 hr. After removal of amine salt by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was crystallized from hexane to give 0.4 g (68%) of *N-tert*-**butyl-2-phenyl-*cis*-2-butenoamide**, mp 106–108°, which was consistent with **25c** obtained in the above experiment.

**Acid-Catalyzed Hydrolysis of 23c.**—A solution of **23c** (2.0 g, 6.25 mmol) in 50 ml of ethanol containing 48% aqueous hydrobromic acid (4 ml) was refluxed for 5 hr. After similar work-up, as described above, the yield of **25c** was 0.68 g (65%).

**Reaction between Di-*tert*-butylsulfur Diimide (1b) and Pentamethyleneketene (2d).**—The reaction was carried out at room temperature for 20 hr as described above using hexahydrobenzoic acid chloride (7.35 g, 0.05 mol), **1b** (3.48 g, 0.02 mol), and triethylamine (6.06 g, 0.06 mol). After similar work-up, the residue obtained was crystallized from hexane to give 1.75 g of *N-tert*-**butyl-1-cyclohexenylcarboxamide** (**25f**): mp 111–112.5°; ir (Nujol) 3320 (NH), 1650 (CO), 1615 (C=C), and 1525 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 1.45–2.30 (m, 8 H), 5.55 (broad, 1 H, NHCO), and 6.50 (broad, 1 H, olefinic proton); mass spectrum (70 eV) *m/e* 181 ($M^+$).

*Anal.* Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.33. Found: C, 72.97; H, 10.87; N, 7.61.

The filtrate was chromatographed on alumina using benzene–hexane as eluent to give 1.5 g of **25f**. The combined yield of **25f** was 3.25 g (89%).

**Reaction between Di-*tert*-butylsulfur Diimide (1b) and Dimethylketene (2c).**—The reaction was carried out at room temperature for 1 hr as described above using isobutyric acid chloride (4.5 g, 0.04 mol), **1b** (3.48 g, 0.02 mol), and triethylamine (4.50 g, 0.0445 mol). After similar work-up, the residue obtained was chromatographed on alumina using benzene–hexane as eluent to give a mixture of *N-tert*-**butyl-2-methylacrylamide** (**25d**) (1.94 g, 69%) and *N-tert*-**butylisobutyramide** (**26d**) (0.26 g, 9%), whose ratio was determined with its nmr spectrum. Recrystallization of the mixture from hexane afforded pure **25d**: mp 50–57° subl; ir (Nujol) 3300 (NH), 1650 (C=O), 1615 (C=C), and 1525 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 1.92 (broad, 3 H, $CH_3C=C<$), 5.23 [broad, 1 H, –(CO)C=C(H)– (trans)] and 5.55 [broad, 2 H, –(CO)C=C(**H**)– (cis) and amide proton]; mass spectrum (70 eV) *m/e* 141 ($M^+$).

*Anal.* Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.80; H, 11.01; N, 9.91.

The filtrate was concentrated and the residue was recrystallized from hexane to give pure **26d**: mp 50–70 subl; ir (Nujol) 3320 (NH), 1640 (CO), and 1545 $cm^{-1}$ (NH); nmr ($CDCl_3$) δ 1.13 (d, 6 H, $CH(CH_3)_2$), 1.85 (s, 9 H, *t*-Bu), 2.23 (m, 1 H, –CH<), and 5.53 (broad, 1 H, NHCO); mass spectrum (70 eV) *m/e* 143 ($M^+$).

*Anal.* Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.76; H, 12.35; N, 9.55.

**Reaction of 23a with 2,3-Dimethylbutadiene.**—A mixture of **23a** (3.40 g, 9.4 mmol) and 2,3-dimethylbutadiene (4.4 ml) in benzene (15 ml) was heated at 140° in a sealed tube for 6 hr. After removal of the resulting **2-phenyl-2-butenoanilide** (**25a**) (1.80 g, 80%) by filtration, the filtrate was evaporated *in vacuo* to yield a brown oil (1.50 g). The oil was distilled to give 0.67 g (35%) of a pale yellow oil, whose structure was identified as **2-phenyl-4,5-dimethyl-3,6-dihydro-1,2-thiazine** (**30**) by comparison of its nmr spectrum with that of an authentic sample:[11] bp 83–85° (0.03 mm) [lit.[11] bp 103–105° (0.1 Torr)]; nmr ($CDCl_3$) δ 1.70 (s, 6 H, $-CH_3$), 2.90 (s, 2 H, $-NCH_2$), 3.90 (s, 2 H, $SCH_2$), 7.0–7.3 (m, 5 H, phenyl protons); mass spectrum (70 eV) *m/e* 205 ($M^+$), 123 (PhN=$S^+$).

**Reaction of 23a with Tetraphenylcyclopentadienone.**—The reaction was carried out as described above using **23a** (3.60 g, 0.01 mol) and tetraphenylcyclopentadienone (3.85 g, 0.01 mol). After removal of solvent, the resulting residue was extracted with hexane, ethanol, and benzene. The hexane extract afforded azobenzene (1.18 g, 65%) and small amounts of oil which were comprised of several components by vpc. The ethanol extract gave 2.1 g (89%) of 2-phenyl-2-butenoanilide. The benzene extract afforded 3.1 g (80%) of starting diene.

**Results of X-Ray Analysis of 4.**—The structure of **4** was unambiguously established through a single-crystal X-ray analysis. The product **4** is unstable and attempts at recrystallization were unsuccessful. Therefore the crystals isolated by adding ether to a concentrated reaction mixture were used for the present X-ray work.

Crystal data follows: $C_{40}H_{30}O_2N_2S \cdot 0.5C_6H_6$, mol wt, 641.9, monoclinic, space group $I2/c$ (No. 15); $a$ = 25.965 (8), $b$ = 10.927 (6), $c$ = 23.932 (9) Å and $\beta$ = 94.83 (3)°, $U$ = 6766 Å$^3$; $D_m$ = 1.25 g/cm$^3$ (flotation method), $D_c$ = 1.26 g/cm$^3$ for $Z$ = 8.

TABLE II

SELECTED BOND LENGTHS (Å) AND ANGLES (DEGREE) IN THE MOLECULE 2,3,4,6,7-PENTAHYDRO-2,4,4,7-TETRAPHENYL-3-OXO-1,5,2,7-THIAOXADIAZEPIN-6-YLIDENEDIPHENYLMETHANE[a]

| Bond | Length, Å | Angle | Degree |
|---|---|---|---|
| S–N(1) | 1.718 (8) | N(1)–S–N(2) | 104.6 (4) |
| S–N(2) | 1.664 (8) | S–N(1)–C(1) | 123.3 (6) |
| N(1)–C(1) | 1.38 (1) | N(1)–C(1)–O(1) | 120.3 (8) |
| C(1)–O(1) | 1.22 (1) | C(2)–C(1)–O(1) | 120.9 (8) |
| C(1)–C(2) | 1.55 (1) | N(1)–C(1)–C(2) | 118.7 (8) |
| C(2)–O(2) | 1.46 (1) | C(1)–C(2)–O(2) | 109.9 (7) |
| C(3)–O(2) | 1.38 (1) | C(2)–O(2)–C(3) | 125.1 (7) |
| C(3)–C(4) | 1.34 (1) | O(2)–C(3)–C(4) | 120.9 (8) |
| N(2)–C(3) | 1.41 (1) | N(2)–C(3)–C(4) | 122.7 (8) |
| | | N(2)–C(3)–O(2) | 115.9 (7) |
| | | S–N(2)–C(3) | 115.1 (6) |

[a] Estimated standard deviations are shown in parentheses.

The three-dimensional intensity data were collected on an automated single-crystal diffractometer. The structure was solved by the parallel use of the direct method and of the heavy atom method, and then refined by the block-diagonal least-squares procedure ($R$ = 0.080 for 2785 observed reflections). Anisotropic temperature factors were assigned for nonhydrogen atoms except those in benzene, for which isotropic temperature factors were used. Isotropic hydrogen atoms were included in the refinement.

The molecule crystallizes with 0.5 mol of benzene. The latter lies on a twofold axis, with a long axis of the molecule parallel to it. The electron density distribution around the benzene molecule is smeared out, probably because of the orientational disorder and/or the low occupancy. Although the refinement might be necessary in this connection, the chemical structure of the product has been well established in view of the low $R$ value. The molecular structure of the molecule viewed along the $b$ axis is shown in Figure 1. The important bond lengths and angles along with estimated standard deviations are listed in Table II.

Other pertinent crystallographic data and parameters may be found in the microfilm edition.[21]

**Registry No.**—**3b**, 36146-94-8; **4**, 36146-93-7; **6a**, 29376-74-7; **6b**, 36146-96-0; **11a**, 36146-97-1; **11b**, 36146-98-2; **12**, 35133-13-2; **13**, 36147-00-9; **15**, 23210-25-5; **16**, 36147-01-0; **17**, 10572-61-9; **18**, 36147-03-2; **19**, 36147-04-3; **23a**, 36138-85-9; **23c**, 36138-86-0; **24b**, 36147-05-4; **24e**, 36147-06-5; **25a**, 36138-87-1; **25b**, 1611-83-2; **25c**, 36138-88-2; **25d**, 6554-73-0; **25e**, 32119-42-9; **25f**, 36147-10-1; **26b**, 4406-41-1; **26c**, 36146-78-8; **26d**, 7472-49-3; **26e**, 2719-26-8; **27a**, 36146-81-3; **28**, 19155-24-9; **31**, 13616-67-6; phenylethylketene, 20452-67-9.

(21) The observed and calculated structure factors, atomic coordinates, and temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-3810. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

# Carbamoyl Chlorosulfines

W. GARY PHILLIPS* AND K. WAYNE RATTS

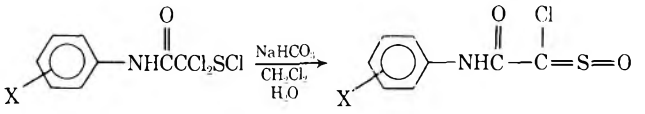
*Monsanto Company, Agricultural and Research Development Department, St. Louis, Missouri 63188*

*Received June 27, 1972*

The synthesis of novel carbamoyl chlorosulfines *via* two different pathways is described. In some cases these reagents slowly convert to a geometrical isomer at room temperature. An assignment of structure to the geometrical isomers is proposed on the basis of physical and spectra data. These sulfines yield α-chloroacetamides upon strong base hydrolysis.

In previous papers we reported that carbamoyldichlorosulfenyl chlorides can be conveniently synthesized[1,2] and that these substances undergo a wide range of reactions.[2] We now wish to report that mild basic hydrolysis of these reagents conveniently yields novel carbamoylchlorosulfines in moderate yield.

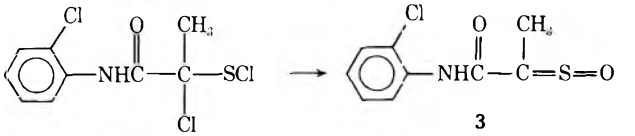
Treatment of **1** with aqueous sodium bicarbonate in a two-phase system employing methylene dichloride as a cosolvent yields carbamoyl chlorosulfines (**2**) in



**1** **2**

**a**, X = 4-Cl
**b**, X = 3-$CF_3$
**c**, X = 3-Br
**d**, X = 4-$OCH_3$
**e**, X = 4-$CH_3$
**f**, X = 2,6-di-$CH_3$
**g**, X = 2-$CH_3$, 6-*t*-$C_4H_9$

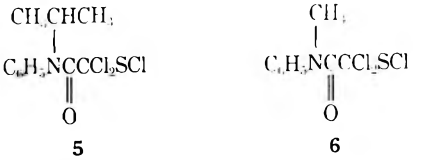
24–57% yield after purification. The reaction is general in that a variety of aromatic substituents may be employed. Water may be substituted for the aqueous bicarbonate although the reaction appears to be slower. In one instance a carbamoyl alkyl sulfine (**3**) was prepared in low yield by hydrolysis of the corresponding sulfenyl chloride (**4**). The only previous



**4** **3**

example of the preparation of a sulfine *via* hydrolysis of a sulfenyl chloride is that of Silhanek and Zbirovsky[3] who reported that dichloromethylene sulfoxide may be prepared by hydrolysis of trichloromethanesulfenyl chloride.

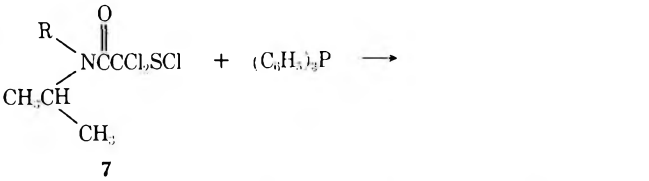
The sequence is not applicable to N,N-disubstituted carbamoyl sulfenyl chlorides. Treatment of **5** with aqueous sodium bicarbonate for 3 days resulted in a high recovery of starting material while **6** slowly yielded



**5** **6**

a mixture of unidentified products from which no sulfine could be isolated.[4]

N,N-Disubstituted carbamoyl chlorosulfines may be prepared by another route. Treatment of N,N-disubstituted carbamoyldichlorosulfenyl chlorides (**7**) with triphenylphosphine yields the corresponding 2-chloro-2-thioxo-*N*,*N*-(disubstituted)acetamide (**8**).[2] Oxidation of these substances with *m*-chloroperbenzoic acid yields the sulfines in moderate yield.



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

**a**, R = $C_6H_5$
**b**, R = *i*-$C_3H_7$

In some cases the sulfines formed *via* the hydrolysis route were thermodynamically unstable. For ex-

(1) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **36**, 3145 (1971).
(2) W. G. Phillips and K. W. Ratts, *ibid.*, **37**, 1526 (1972).
(3) J. Silhanek and M. Zbirovsky, *Chem. Commun.*, 878 (1969).
(4) Attempts to extend this synthetic route to other sulfenyl chlorides failed; hydrolysis of phenylsulfonyldichloromethylsulfenyl chloride with weak base yielded no reaction while hydrolysis of cyanodichloromethylsulfenyl chloride yielded α-chloroacetonitrile.

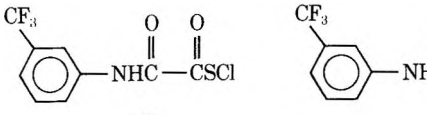
ample, **2b** was found to rearrange to a monomeric isomer **10** with a half-life of about 1 week at room temperature. The reaction was easily followed by observing the disappearance of the strong band at 1015 $cm^{-1}$ in the infrared spectrum of **2b**.

The infrared and ultraviolet spectral data for the two isomers are shown in Table I. The carbonyl

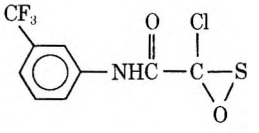
TABLE I
SPECTRAL DATA FOR **2b** AND **10**

| | **2b** | **10** |
|---|---|---|
| Ir ($CDCl_3$), $cm^{-1}$ | 1695 (C=O) | 1670 (C=O) |
| | 3360 (N-H) | 3445 (N—H) |
| | 1015 | No band at 1015 |
| Uv ($CH_3CN$), mμ (ε) | $\tau_{max}$ 228 (6488), 288 (4384) | $\tau_{max}$ 230 (6422), 302 (6922) |

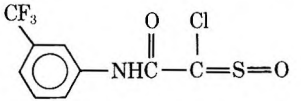
frequency suggested that the isomer must be **11**, **12**, or **13**.[5,6]



**11**



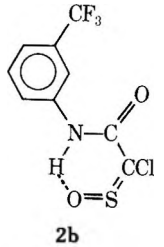
**12**



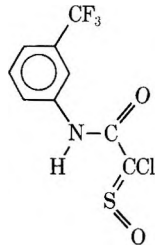
geometrical isomer
**13**

The sulfenyl chloride **11** could be ruled out by comparison with an authentic sample.[2] The ultraviolet spectrum of **10** eliminates **12** from consideration; **12** would not be expected to have a band at 302 mμ. Thus one can conclude that **2b** slowly converts to a geometrical isomer.

Information suggesting an assignment of configuration has been obtained. An examination of models of the two geometrical isomers suggests that intramolecular hydrogen bonding can readily occur in one of the configurations. Since **2b** is considerably more volatile than **10**,[7] this suggests that **2b** and **10** have the configurations shown below. Their infrared spectra



**2b**

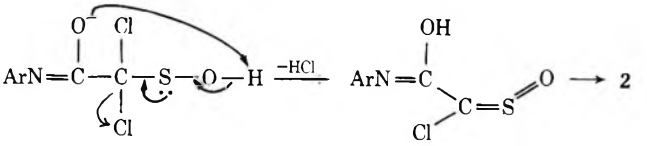


**10**

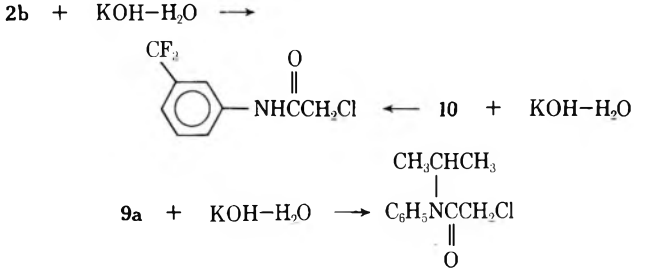
also support this conclusion. The N-H frequency of **2b** is lower than that of **10** and is in the range for a hydrogen bonded N-H.[8] Also **2b** would be expected to have a higher carbonyl frequency than **10** since its carbonyl is forced to become coplanar with a chlorine atom.

Analogously **2d** also was found to undergo an isomerization upon heating. A higher melting compound (**14**) was formed which had a higher N-H band and a lower carbonyl band in its infrared spectrum.

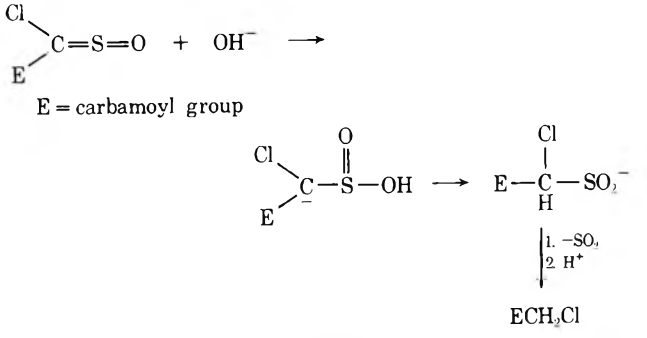
The mechanism of the mild basic hydrolysis of α,α-dichlorosulfenyl chlorides is not known. However, it is tempting to speculate that a sulfenic acid is first formed which loses hydrogen chloride *via* an internal base. This would account for the observed stereochemistry of the initial sulfine.



The carbamoyl chlorosulfines have been found to yield α-chloroacetanilides in good yield upon treatment with strong base. A likely mechanism involves Michael addition of hydroxide ion to the sulfine to

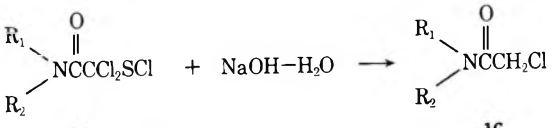


yield a sulfinic acid which can lose sulfur dioxide to yield α-chloroacetanilide. The only previous example of a Michael addition to a sulfine is that of Schultz



and Schlessinger[9] who found that treatment of diarylsulfines with methyllithium gave methyl sulfoxides.

Direct strong basic hydrolysis of the carbamoyldichloromethylsulfenyl chlorides also yields α-chloroacetamides. Presumably a carbamoyl chlorosulfine is an intermediate in these reactions.



**15** **16**

**a**, $R_1 = C_6H_5$; $R_2 = i\text{-}C_3H_7$
**b**, $R_1 = i\text{-}C_3H_7 = R_2$
**c**, $R_1 = H$; $R_2 = 2\text{-}CH_3\text{-}6\text{-}t\text{-}C_4H_9C_6H_3$
**d**, $R_1 = 2,6\text{-}(C_2H_5)_2C_6H_3$; $R_2 = CH_2OCH_3$

(5) The bent nature of the C=S=O group is well established, King and Durst[6] have succeeded in isolating the two isomers oxythiobenzoyl chlorides by fractional crystallization and proposed assignment of configurations on the basis of dipole moment.

(6) J. F. King and T. Durst, *J. Amer. Chem. Soc.*, **85**, 2676 (1963).

(7) Compound **2b** volatilizes into the mass spectrograph at 40° while **10** does not produce an ion current until 220° is reached.

(8) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207.

(9) A. G. Schultz and R. H. Schlessinger, *Chem. Commun.*, 747 (1970).

## Experimental Section

Melting points are uncorrected. Infrared spectra as chloroform solutions were determined on a Beckman IR-5A instrument. Nmr spectra were determined on a Varian A-60 or T-60 instrument. Procedures for the preparation of the sulfenyl chlorides are described in our earlier papers.[1,2]

**General Procedure for Preparation of Carbamoyl Chlorosulfines *via* Hydrolysis Route (Method A).**—To one part by weight of the appropriate $\alpha,\alpha$-dichlorosulfenyl chloride in methylene chloride was added one part of sodium bicarbonate in water. The volumes of methylene chloride and of water were approximately equal. After stirring vigorously *ca.* 0.5 hr, the layers were separated; the organic layer was dried ($MgSO_4$). Removal of the solvent gave a mass which was triturated with a small amount of ether. Collection of the solid generally gave a pure product although the product could usually be recrystallized from petroleum ether (bp 30–75°) (see Table II).

TABLE II

CARBAMOYL CHLOROSULFINES[a]

| No. | Mp, °C | Yield, % | Synthesis method |
|---|---|---|---|
| **2a** | 111–113 | 49 | A |
| **2b** | 89–91[b] | 57 | A |
| **2c** | 110–111 | 52 | A |
| **2d** | 98[c] | 50 | A |
| **2e** | 95–98 | 26 | A |
| **2f** | 101–109 | 52 | A |
| **2g** | 168–169 | 42 | A |
| **3** | 103–105 | 8 | A |
| **9a** | 48–55[d] | 19 | B |
| **9b** | 47–51 | 79 | B |
| **10**[e] | 139–140 | 50 | ... |
| **14**[f] | 143–145 | 80 | ... |

[a] Satisfactory analytical values (±0.25% for C, H, and N) were reported for all compounds. [b] This product melts at 89–91° and resolidifies and melts again at *ca.* 120°. The mass spectrum showed a molecular ion at 283 and a base peak at 235 ($M^+ - SO$). The molecular weight in benzene was 333 (calcd 284). [c] This product melts at 98° and resolidifies and melts again at 137–140°. [d] Mass spectra data: 267 ($M^+$); 209 ($M^+ - SO$, base peak). [e] Prepared by heating **2b** on a steam bath for 0.5 hr; the molecular weight in benzene was 293 (calcd 284). [f] Prepared by heating **2d** on a steam bath for 0.5 hr.

**Preparation of Carbamoyl Chlorosulfines *via* Oxidation of the Corresponding 2-Chloro-2-thioxoacetamide (Method B).**—To 1 equiv of the 2-chloro-2-thioxoacetamide[2] in methylene chloride was added 0.95 equiv of *m*-chloroperbenzoic acid (exothermic). The red color was immediately discharged. After 0.5 hr of stirring the *m*-chlorobenzoic acid was filtered and the resulting solution extracted with a cold, dilute, aqueous sodium bicarbonate solution. Removal of the solvent gave an oil which was taken up in pentane. Cooling of the pentane solution in Dry Ice gave a solid (see Table II).

**Attempted Hydrolysis of $\alpha$-(*N*-Phenyl-*N*-isopropylcarbamoyl)-$\alpha,\alpha$-dichloromethylsulfenyl Chloride.**—The general procedure of sodium bicarbonate hydrolysis of $\alpha,\alpha$-dichlorosulfenyl chlorides was followed except that a reaction time of 3 days was employed. The recovery of starting material was 90%, mp 121–123° (lit.[1] mp 121–122°). Its ir spectrum was identical with that of **5**.

**Attempted Hydrolysis of $\alpha$-Phenylsulfenyl-$\alpha,\alpha$-dichloromethylsulfenyl Chloride.**—The general procedure for the sodium bicarbonate hydrolysis of sulfenyl chlorides was followed. A 65% yield of starting material was recovered. The product had the same ir as that of starting sulfenyl chloride, mp 52–57° (lit.[1] mp 62–64°).

**Hydrolysis of $\alpha$-Cyano-$\alpha,\alpha$-dichloromethylsulfenyl Chloride.**—The general procedure for the sodium bicarbonate hydrolysis of sulfenyl chlorides was employed except that water was used in place of the bicarbonate solution. The product was distilled at 118–120° and had an ir spectrum identical with that of chloroacetonitrile, yield 37%.

**General Procedure for Hydrolysis of Carbamoyl Chlorosulfines.**—To 1 equiv of the sulfine in methanol was added *ca.* 10 equiv of sodium hydroxide solution. The volumes of methanol and water were approximately equal. After the solution was stirred 0.5 hr, concentrated hydrochloric acid was added until the solution became acidic. After standing *ca.* 1 hr the $\alpha$-chloroacetamide was filtered and recrystallized from petroleum ether. When **9a** was employed, *N*-isopropyl-$\alpha$-chloroacetanilide was obtained in 66% yield: mp 67–68°; nmr ($CDCl_3$) $\tau$ 2.5 (m, 5), 5.1 (h, 1), 6.3 (s, 2), 8.9 (d, 6). Its ir spectrum was identical with that of authentic material (Monsanto). When **2b** or **10** was employed as the sulfine, yields of 59 and 41%, respectively, of *m*-trifluoromethyl-$\alpha$-chloroacetanilide were obtained: mp 69–70°; nmr ($CDCl_3$) $\tau$ 2.4 (m, 4), 5.9 (s, 2). The melting point of authentic material prepared from *m*-trifluoromethylaniline and chloroacetyl chloride was 74–75°.

**General Procedure for the Potassium Hydroxide Hydrolysis of $\alpha,\alpha$-Dichlorosulfenyl Chlorides.**—To 10 mmol of **9a** in 50 ml of methanol was added 100 ml of 10% potassium hydroxide. After heating to 75°, the solution was acidified with concentrated hydrochloric acid. Cooling the mixture gave a 78% yield of *N*-isopropyl-$\alpha$-chloroacetanilide (**16a**), mp 70–71° (petroleum ether).

*Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.21; H, 6.60. Found: C, 62.01; H, 6.81.

In a similar manner **16b** was prepared from **15b** in 52% yield; **16c** was prepared from **15c** in 60% yield; **16d** was prepared from **15d** in 73% yield. In these cases, product identification was made on the basis of the nmr spectra.

**Registry No.**—**2a**, 36287-02-2; **2b**, 36287-03-3; **2c**, 36287-04-4; **2d**, 36287-05-5; **2e**, 36287-06-6; **2f**, 36287-07-7; **2g**, 36287-08-8; **3**, 36287-09-9; **9a**, 36287-10-2; **9b**, 36287-11-3; **10**, 36287-12-4; **14**, 36208-06-7; **16a**, 1918-16-7; *m*-trifluoromethyl-$\alpha$-chloroacetanilide, 351-38-2.

# *S*-Aroyl-, *S*-Thioaroyl-, and *S*-Imidoylhydrosulfamines

MAYNARD S. RAASCH

*Contribution No. 1910 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898*

*Received May 25, 1972*

Amination of sodium salts of aromatic thio acids with sodium hydroxylamine-*O*-sulfonate forms stable *S*-aroylhydrosulfamines, $ArCOSNH_2$. The thio analogs, $ArCSSNH_2$, and *N*-phenylimino analogs, $RC(=NC_6H_5)SNH_2$, are less stable. Reaction with isocyanates gives stable ureas. Cyclic imides and Schiff bases with salicylaldehyde have also been made.

*S*-Aroylhydrosulfamines, a new type of derivative, may be made simply by mixing aqueous solutions of sodium hydroxylamine-*O*-sulfonate and the sodium salt of an aromatic thio acid and filtering off the product. Surprisingly, these compounds are, in general, stable to recrystallization, storage, and reaction with other reagents.

Previous attempts to make *S*-acylhydrosulfamines

TABLE I

*S*-AROYL-, *S*-THIOAROYL-, AND *S*-IMIDOYLHYDROSULFAMINES[a,b]

| No. | Compd | Registry no. | Yield, % | Recrystn solvent | Mp, °C | Pmr ($CDCl_3$), $NH_2$, ppm |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5COSNH_2$ | 25740-80-1 | 90 | $Et_2O$ | 88.5–90 | 2.47 |
| 2 | 3,4-$Cl_2C_6H_3COSNH_2$ | 35124-68-6 | 95 | $CH_2Cl_2$ | 119–120 | 2.83 |
| 3 | *p*-$O_2NC_6H_4COSNH_2$ | 35124-67-5 | 41 | $CHCl_3$ | 113–114 | 1.90 |
| 4 | *p*-$CH_3OC_6H_4COSNH_2$ | 35124-66-4 | 94 | $Et_2O$ | 99–100 | 2.78 |
| 5 | *p*-$H_2NSCOC_6H_4COSNH_2$ | 35124-69-7 | 81 | $CH_3CN$[c] | 185 dec[c] | |
| 6 | 1-Naphthoyl-$SNH_2$ | 35124-65-3 | 93 | $CCl_4$ | 76.5–77 | 3.05 |
| 7 | 2-Furoyl-$SNH_2$ | 35124-70-0 | 70 | $CCl_4$ | 60–61 | 2.90 |
| 8 | $C_6H_5CSSNH_2$ | 35124-71-1 | 84 | Pentane | 29 | 3.21 |
| 9 | *p*-$ClC_6H_4CSSNH_2$ | 35124-72-2 | 87 | Hexane | 60–61 | 3.31 |
| 10 | $CH_3C(=NC_6H_5)SNH_2$ | 35124-73-3 | 88 | $CH_3OH$ | 69.5–71 | 2.98 |
| 11 | $C_6H_5C(=NC_6H_5)SNH_2$ | 35124-74-4 | 94 | Cyclohexane | 68–69 | 2.99 |

[a] M. S. Raasch, U. S. Patent 3,631,071 (1971). [b] Satisfactory analytical data (±0.40% for C, H, and N) were reported for all compounds listed in the table: Ed. [c] Low solubility; melting point determined by placing on hot block.

$$ArCOSNa + H_2NOSO_3Na \longrightarrow ArC(=O)SNH_2 + Na_2SO_4$$

have been recorded. Reaction of $CH_3COSCl$ with diethylamine gave a product, presumably $CH_3COSN(C_2H_5)_2$, which soon decomposed to sulfur and diethylacetamide. Piperidine gave similar results. From aniline, the oil obtained, $CH_3COSNHC_6H_5$, underwent 50% decomposition in 24 hr at 3–5° and complete decomposition in 3 days.[1] Further, oxidative coupling of cyclohexylamine with ArCOSNa or ArCSSNa produced the amide or thioamide and sulfur. The reaction was postulated to proceed through the unstable *N*-cyclohexyl-*S*-aroylhydrosulfamine.[2]

The reported instability of *S*-acylhydrosulfamines and *N*-alkyl-*S*-aroylhydrosulfamines is in agreement with the present work. Reaction of sodium hydroxylamine-*O*-sulfonate with sodium thioacetate gave an immediate precipitation of sulfur. Similarly, sodium *N*-methylhydroxylamine-*O*-sulfonate[3] and sodium thiobenzoate resulted in a 90% yield of sulfur and *N*-methylbenzamide. Sodium 3,4-dichlorothiobenzoate reacted in the same manner. Sodium thionicotinate[4] and sodium hydroxylamine-*O*-sulfonate gave sulfur and nicotanamide. Thus, *S*-nicotinoylhydrosulfamine is also unstable.

Examples of *S*-aroylhydrosulfamines are listed in Table I (1–7). The *p*-nitro derivative is the least stable. Its preparation in 41% yield is accompanied by a 37% yield of *p*-nitrobenzamide from decomposition. The rest are stable except that the furoyl compound decomposes on long storage at 24°. The relative stability of the compounds was estimated by placing a melting point capillary tube containing the compound in a bath at 190° and noting the number of seconds required for the melt to become cloudy because of the liberation of sulfur. Exact times are subject to reservations as they appear to be influenced by catalytic amounts of impurities, but the times observed were *p*-$O_2NC_6H_4$, 6 sec; 2-furyl, 52; $C_6H_5$, 120; *p*-$CH_3OC_6H_4$, 250; 1-naphthyl, 373. For 3,4-$Cl_2C_6H_3$, all the sulfur stayed in solution.

**S-Thioaroylhydrosulfamines.**—The two thioaroyl analogs, $C_6H_5CSSNH_2$ and *p*-$ClC_6H_4CSSNH_2$, in Table I are less stable than any of the carbonyl compounds. Of the two, the *p*-chloro compound is the more stable. Both can be stored at −78°. Compounds of the type $ROCSSNH_2$, from sodium xanthates and sodium hydroxylamine-*O*-sulfonate, have been reported.[5] They are unstable. However, $(CH_3)_2NCSSNH_2$ from sodium dimethyldithiocarbamate and chloramine[6,7] or ammonia plus sodium hypochlorite[7] will last for months at 24°. This compound can also be made conveniently by using sodium hydroxylamine-*O*-sulfonate as the aminating agent.

**S-Imidoylhydrosulfamines.**—An imino analog, $C_6H_5C(=NC_6H_5)SNH_2$, of the *S*-aroyl- and *S*-thioaroylhydrosulfamines was synthesized by dissolving thiobenzanilide in aqueous sodium hydroxide and adding sodium hydroxylamine-*O*-sulfonate. The compound can be kept at 4°. From thioacetanilide $CH_3C(=NC_6H_5)SNH_2$ can be made but is less stable. The oxidative amination of substituted thioureas and thiourethanes with amines to form compounds of the type $R_2NC(=NR^1)SNR^2R^3$ and $ROC(=NR^1)SNR^2R^3$ has been reported.[8]

**Derivatives.**—The *S*-aroyl-, *S*-thioaroyl-, and *S*-imidoylhydrosulfamines react with isocyanates to form ureas (eq 1). These derivatives are stable, even those

$$RC(=X)SNH_2 \xrightarrow{R^1NCO} RC(=X)SNHCONHR^1 \quad (1)$$
$$X = O, S, NC_6H_5$$

prepared from unstable starting materials. Examples are listed in Table II.

Schiff bases have been formed from salicylaldehyde (eq 2 and 3). With *p*-$ClC_6H_4CSSNH_2$, however, a 76% yield of sulfur was obtained.

With *S*-aroylhydrosulfamines, amic acids and cyclic imides have been obtained from cyclic anhydrides, *e.g.*,

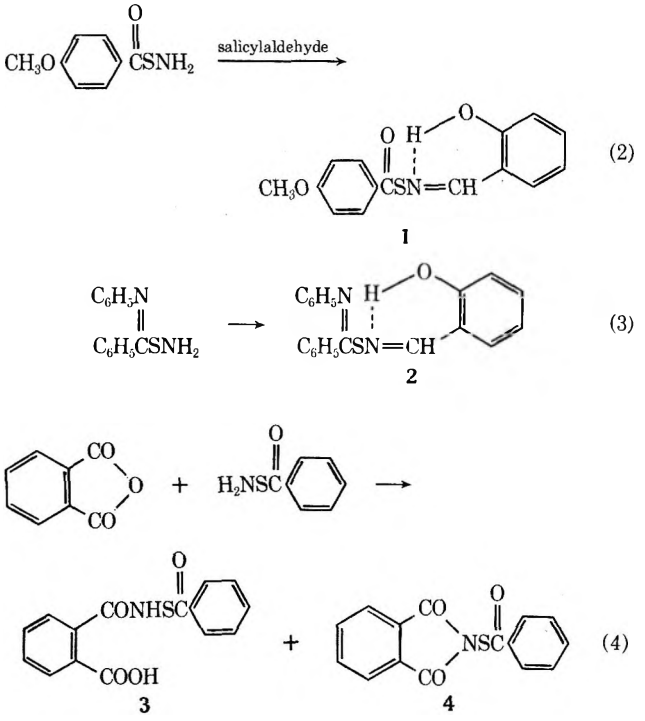
(1) H. Böhme and M. Clement, *Justus Liebigs Ann. Chem.*, **576**, 61 (1952).
(2) G. Alliger, G. E. P. Smith, Jr., E. L. Carr, and H. P. Stevens, *J. Org. Chem.* **14**, 962 (1949).
(3) E. Schmitz, R. Ohme, and D. Murawski, *Chem. Ber.*, **98**, 2516 (1965).
(4) A. M. Grigorovskii and Z. M. Kimen, *Z. Obshch. Khim.* **18**, 171 (1948); *Chem. Abstr.*, **42**, 7296 (1948).
(5) R. Gösl, *Angew. Chem.*, **74**, 329 (1962); *Angew. Chem., Int. Ed. Engl.*, **1**, 268 (1962); R. Gösl and A. Meuwsen, *Z. Anorg. Allg. Chem.*, **314**, 334 (1962), aminated sodium thiosulfate with sodium hydroxylamine-*O*-sulfonate to form $H_2NSSO_3Na$.
(6) R. S. Hanslick, U. S. Patent 2,318,482 (1943); *Chem. Abstr.*, **37**, 6159 (1943).
(7) G. E. P. Smith, Jr., G. Alliger, E. L. Carr, and K. C. Young, *J. Org. Chem.*, **14**, 935 (1949).
(8) K. Ley and U. Eholzer, *Angew. Chem.*, **78**, 672 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 674 (1966); German Patent 1,255,654 (1967); *Chem. Abstr.*, **68**, 87302*a* (1968); U. Eholzer, K. Ley, G. Zumach, L. Eue, and E. Hack, British Patent 1,074,760 (1968); *Chem. Abstr.*, **65**, 13605*b* (1966); H. Huckstadt, U. Eholzer, F. Moll, W. Himmelmann, and K. Ley, British Patent 1,129,356 (1968); *Chem. Abstr.*, **66**, 110062*s* (1967); D. Duerr, German Patent 1,936,459 (1970); *Chem. Abstr.*, **72**, 90119*j* (1970).

TABLE II

UREAS FROM REACTION WITH ISOCYANATES[a]

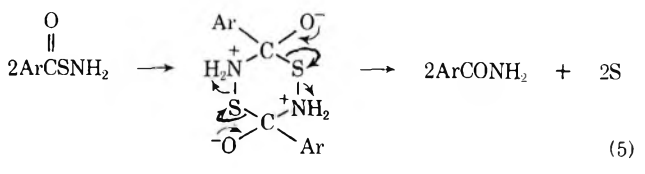
| Compd | Registry no. | Recrystn solvent | Yield, % | Mp, °C |
|---|---|---|---|---|
| $C_6H_5COSNHCONHC_6H_5$ | 36504-30-0 | Acetone | 90 | 192.5–194 |
| $C_6H_5COSNHCONH$-$p$-$C_6H_4Cl$ | 36504-31-1 | Acetone | 96 | 199–199.5 |
| $C_6H_5COSNHCONHCH_3$ | 36504-32-2 | Dioxane | 69 | 194–195.5 |
| $3,4$-$Cl_2C_6H_3COSNHCONHCH_3$ | 36504-33-3 | Dioxane | 98 | 195–196 |
| $C_6H_5CSSNHCONHC_6H_5$ | 36504-34-4 | Dioxane | 88 | 179–180 |
| $CH_3C(=NC_6H_5)SNHCONH$-$p$-$C_6H_4Cl$ | 36504-35-5 | $CH_2Cl_2$ | 70 | 134–136 |
| $C_6H_5C(=NC_6H_5)SNHCONHCH_3$ | 36504-36-6 | EtOAc | 78 | 141.5–142 |

[a] Satisfactory analytical data (±0.38% for C, H, and N) were reported for all compounds listed in the table: Ed.



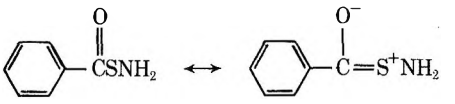

eq 4. 4-Cyclohexene-1,2-dicarboxylic and dichloromaleic anhydrides are also operable.

**Discussion of Stability.**—The decomposition of the *S*-aroylhydrosulfamines to amide and sulfur could occur by a unimolecular homolytic or heterolytic mechanism, but we favor a bimolecular process involving a cyclic intermediate or transition state which could decompose in a concerted manner to expel sulfur and form the amide (eq 5). Such a mechanism would be expected to



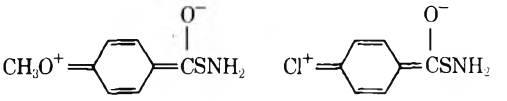

show substituent effects analogous to basic hydrolysis of esters as one factor affecting stability. The *p*-nitro group, for example, markedly reduces stability. The more basic *N*-methyl derivatives might form the transition state more readily, causing the observed instability, whereas *N*-acyl derivatives are more stable than the parent compounds. In the case of compounds of the type $ArC(=S)SNH_2$, the preference of sulfur to be singly bonded would favor the transition state and result in the observed lower stability compared to the carbonyl compounds.

The fact that *S*-aroylhydrosulfamines are stable in contrast to their aliphatic analogs can be rationalized by the additional resonance conjugation

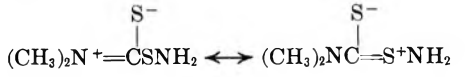


Electron donation by *N*-methyl lessens the contribution of the sulfonium form and results in instability while N-acylation has the reverse effect.

In the case of *p*-methoxy and *p*-chloro derivatives, an additional resonance form is favorable.



These representations can be regarded as vinylogous to the thioamide type of stabilization which probably occurs with $(CH_3)_2NCSSNH_2$ to make it more stable than $ArCSSNH_2$.



## Experimental Section

The $^1H$ nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as internal standard. The ir spectra were measured on Perkin-Elmer Model 21. Melting points are uncorrected.

**Monothio Acids.**—Except for thiobenzoic acid and dithioterephthalic acid, which can be purchased, the thio acids were made by the procedure of Noble and Tarbell.[9] In preparing thionicotinic acid,[4] the reaction was run at −20°. The acid was precipitated with acetic acid and recrystallized from 50% ethanol, yield 43%. *p*-Thioanisic,[10] *p*-nitrothiobenzoic,[11] 1-thionaphthoic,[12] and 2-thiofuroic[13] acids have been reported previously. 3,4-Dichlorothiobenzoic acid is new, mp 73.5–75° from $CCl_4$.

*Anal.* Calcd for $C_7H_4Cl_2OS$: C, 40.58; H, 1.95; S, 15.48. Found: C, 40.84; H, 1.96; S, 15.04.

***S*-Aroylhydrosulfamines (Table I).**—The general procedure was to prepare a *ca.* 30% solution of sodium hydroxylamine-*O*-sulfonate by neutralizing an aqueous solution of the acid with aqueous sodium hydroxide below 20°. This was added slowly to a *ca.* 15%, mechanically stirred solution of the sodium salt of the thio acid below 20° until no more precipitation occurred. The product was filtered and air-dried. The yields before recrystallization appear in the table. In the case of the preparation of *S*-(*p*-nitrobenzoyl)hydrosulfamine, the dried product mixture was stirred with chloroform, and *p*-nitrobenzamide was filtered. The product was crystallized from the filtrate with a minimum of heating for concentration: ir for $C_6H_5COSNH_2$ 3333, 3268

(9) P. Noble, Jr., and D. S. Tarbell in "Organic Syntheses," Collect. Vol IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, pp 924–927.

(10) I. Bloch and M. Bergmann, *Ber. Deut. Chem. Ges. B*, **53**, 961 (1920).

(11) A. M. Khaletskii and A. M. Yanovitskaya, *Z. Obshch. Khim.*, **19**, 1193 (1949); *J. Gen. Chem. USSR*, **19**, 1187 (1949).

(12) S. I. Sergievskaya and A. A. Kropacheva, *Z. Obshch. Khim.*, **10**, 1737 (1940); *Chem. Abstr.*, **35**, 4003 (1941).

(13) S. Patton, *J. Amer. Chem. Soc.*, **71**, 3571 (1949).

$cm^{-1}$ ($NH_2$), 1658 (C=O), 1595, 1580, 1488 (aromatic C=C), 689 (monosubstituted aromatic).

*S*-**Thiobenzoylhydrosulfamine** (**Table I**).—An alcoholic solution of potassium dithiobenzoate was prepared from benzotrichloride and potassium sulfide according to the directions of Kurzer and Lawson.[14] The alcohol was removed under reduced pressure, and the residual salt was dissolved in 200 ml of water and extracted with ether. The aqueous layer was separated and acidified with 25 ml of 37% hydrochloric acid. The dithiobenzoic acid was collected with two 150-ml portions of ether and dried ($Na_2SO_4$), and the ether was removed to leave 25 g of a purple oil. This crude dithiobenzoic acid was aminated according to the general procedure described above. The orange, crystalline *S*-thiobenzoylhydrosulfamine was filtered while the aqueous phase was at 15°, yield 23 g. It can be stored at −78°.

*S*-(*p*-**Chlorothiobenzoyl**)**hydrosulfamine** (**Table I**).—Crystalline *p*-chlorodithiobenzoic acid[15] was prepared according to the procedure used for dithiobenzoic acid except that *p*-chlorobenzotrichloride was used, yield 66%. It was aminated in the usual way: ir of *p*-$ClC_6H_4CSSNH_2$ 3300, 3205 $cm^{-1}$ ($NH_2$), 3077 (=CH), 1590, 1481 (aromatic C=C), 830 (para-disubstituted aromatic). The compound can be stored at −78°.

*S*-(*N*-**Phenylacetimidoyl**)**hydrosulfamine** (**Table I**).—Thioacetanilide (25 g, 0.166 mol) was dissolved in 200 ml of water containing 7 g (0.175 mol) of sodium hydroxide. Addition below 20° of 22.6 g (0.2 mol) of hydroxylamine-*O*-sulfonic acid in 45 ml of water neutralized below 20° with 8 g (0.2 mol) of sodium hydroxide in 45 ml of water caused precipitation of the product. This unstable compound was filtered and blotted on paper, yield 24 g. An analytical sample was quickly recrystallized from methanol. The compound can be stored at −78°: $^1H$ nmr ($CDCl_3$) 1.93 ppm (s, $CH_3$), 2.98 (s, broad, $NH_2$, removed by $D_2O$), 6.7–7.5 (m, $C_6H_5$).

*S*-(*N*-**Phenylbenzimidoyl**)**hydrosulfamine** (**Table I**).—Thiobenzanilide (42.7 g, 0.2 mol) was dissolved in 400 ml of water containing 16 g (0.4 mol) of sodium hydroxide. Amination was accomplished by adding below 20° with stirring a solution of 27 g (0.24 mol) of hydroxylamine-*O*-sulfonic acid in 60 ml of water neutralized with 9.6 g (0.24 mol) of sodium hydroxide in 60 ml of water. The initial addition produced a sticky precipitate which was scratched to provide seed crystals. The product was filtered and air-dried to give 43 g (94%). Recrystallization twice from cyclohexane left 28 g (61%), mp 68–69°. An additional 5 g (11%) was isolated from the mother liquor: ir 3311, 3145 $cm^{-1}$ ($NH_2$), 3058, 3012 (=CH), 1616 (C=N), 1585, 1572, 1479 (aromatic C=C), 770–667 (monosubstituted aromatic); Raman 1621 $cm^{-1}$ (C=N), 1592 (aromatic C=C). This compound decomposes in days or weeks at 24°, the rate being dependent on purity. The decomposition products are sulfur and benzamidine, mp 115–116°.

**Ureas** (**Table II**).—The reaction of the hydrosulfamines with isocyanates was carried out in dichloromethane. After 20 hr the precipitated urea was filtered. The mother liquid was concentrated in some cases to obtain more product. Yields before recrystallization are recorded in the table: $^1H$ nmr for $C_6H_5COSNHCONHC_6H_5[(CD_3)_2SO]$ 6.6–7.9 ppm (m, 2 $C_6H_5$), 7.84 (s, NHS), 8.94 (s, NHCO). The NH peaks were removed by $D_2O$.

*S*-(*p*-**Anisoyl**)-*N*-**salicylidenehydrosulfamine** (**1**).—*S*-(*p*-Anisoyl)hydrosulfamine (3.66 g, 0.02 mol) and 2.44 g (0.02 mol) of salicylaldehyde were heated on a steam bath for 30 min. The mixture first melted and then solidified. Recrystallization from dioxane gave 4.9 g (85%) of the Schiff base, mp 186–187.5°.

*Anal.* Calcd for $C_{15}H_{13}NO_3S$: C, 62.68; H, 4.56; S, 11.16. Found: C, 62.45; H, 4.60; S, 11.06.

(14) F. Kurzer and A. Lawson, *Org. Syn.*, **42**, 100 (1942).

(15) F. Becke and H. Hagen, German Patent 1,274,121 (1968); *Chem. Abstr.*, **70**, 3573v (1969); R. Mayer and S. Scheithauer, *Chem. Ber.*, **98**, 829 (1965); K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1087 (1961).

*S*-(*N*-**Phenylbenzimidoyl**)-*N*-**salicylidenehydrosulfamine** (**2**).—*S*-(*N*-Phenylbenzimidoyl)hydrosulfamine (4.56 g, 0.02 mol) and 2.44 g (0.02 mol) of salicylaldehyde were heated on a steam bath for 30 min. The resulting solid was recrystallized from carbon tetrachloride to give 4.22 g (64%) of the Schiff base, mp 139–139.5°.

*Anal.* Calcd for $C_{20}H_{16}N_2OS$: C, 72.25; H, 4.85; N, 8.43. Found: C, 71.96; H, 4.73; N, 8.37.

*N*-(**Benzoylthio**)**phthalimide** (**4**) **and** *N*-(**Benzoylthio**)**phthalamic Acid** (**3**).—To 8.9 g (0.06 mol) of phthalic anhydride dissolved in in 30 ml of warm tetrahydrofuran was added 9.2 g (0.06 mol) of *S*-benzoylhydrosulfamine in 20 ml of tetrahydrofuran. The solution was refluxed for 30 min, and the solvent was then allowed to evaporate. The resulting crystals were rinsed with carbon tetrachloride, dried, and stirred with 5% sodium bicarbonate solution. The phthalimide was filtered, yield 8.3 g (49%). Recrystallization from acetone left 7.1 g, mp 150–151°.

*Anal.* Calcd for $C_{15}H_9NO_3S$: C, 63.63; H, 3.20; S, 11.32. Found: C, 63.82; H, 3.27; S, 11.16.

The sodium bicarbonate filtrate was acidified with hydrochloric acid and the *N*-(benzoylthio)phthalamic acid was filtered, washed with water, and air-dried, yield 5.3 g (29.5%). Recrystallization from acetone gave 4.1 g in two crops, mp 144–144.5°, with conversion into the phthalimide.

*Anal.* Calcd for $C_{15}H_{11}NO_4S$: C, 59.78; H, 3.68; S, 10.64. Found: C, 59.86; H, 3.76; S, 10.81.

6-[(**1-Naphthoylthio**)**carbamoyl**]-**3-cyclohexene-1-carboxylic Acid**.—*S*-(1-Naphthoyl)hydrosulfamine (6.09 g, 0.03 mol) in 25 ml of chloroform was added to 4.56 g (0.03 mol) of 4-cyclohexene-1,2-dicarboxylic anhydride in 25 ml of chloroform, and the solution was refluxed for 1 hr. From the cooled solution, 7.96 g (75%) of the amic acid was filtered. It was completely soluble in 5% sodium bicarbonate. Recrystallization from acetone left 6.1 g mp 172.5–173°.

*Anal.* Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.20; H, 4.86; N, 3.86.

*N*-(**1-Naphthoylthio**)-**4-cyclohexene-1,2-dicarboximide**.—The above amic acid (5.33 g, 0.15 mol), 10 ml of pyridine, and 1.6 ml (0.017 mol) of acetic anhydride were mixed and allowed to stand 1 hr. The solution was poured into water, and the crystals were filtered and air-dried. The product was taken up in acetone, and 0.8 g of insoluble material was filtered. The acetone was evaporated, and the residue was recrystallized twice from ethanol to give 3.5 g (70%) of the imide, mp 96–98°.

*Anal.* Calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15. Found: C, 67.31; H, 4.46; N, 4.00.

*N*-(**3,4-Dichlorobenzoylthio**)**dichloromaleimide**.—Dichloromaleic anhydride (2.50 g, 0.015 mol), 3.33 g (0.015 mol) of *S*-(3,4-dichlorobenzoyl)hydrosulfamine, and 10 ml of benzene were heated under reflux on a steam bath for 30 min, then 2 hr with the condenser removed. The residue was recrystallized twice from cyclohexane to give 4.02 g (71%) of the imide, mp 89–91°.

*Anal.* Calcd for $C_{11}H_3Cl_4NO_3S$: C, 35.61; H, 0.82; N, 3.78. Found: C, 35.62; H, 0.82; N, 3.72.

**Registry No.**—**1**, 36504-37-7; **2**, 36504-38-8; **3**, 36504-39-9; **4**, 36504-40-2; 6-[(1-naphthoylthio)-carbamoyl]-3-cyclohexene-1-carboxylic acid, 36504-41-3; *N*-(1-naphothylthio)-4-cyclohexene-1,2-dicarboximide, 36504-42-4; *N*-(3,4-dichlorobenzoylthio)dichloromaleimide, 36504-43-5; 3,4-dichlorothiobenzoic acid, 36504-44-6.

**Acknowledgment.**—The author is indebted to Dr. W. A. Sheppard for helpful discussions.

# Seven-Membered Heterocycles. IV. The 5-Hydroxy-2-chloro-4,5-dihydro-1-benzothiepin System[1a,b]

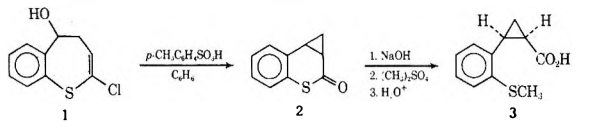
VINCENT J. TRAYNELIS*[1c] AND DAN M. BORGNAES[1d]

*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556*

*Received May 30, 1972*

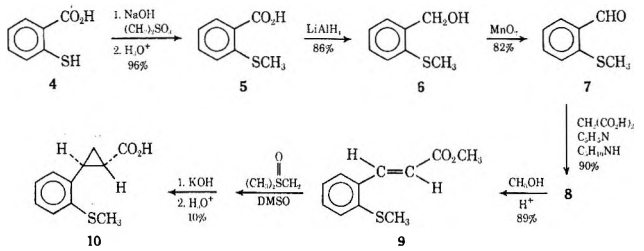
The synthesis of *trans*-2-(2-methylthiophenyl)cyclopropanecarboxylic acid (**10**) is described with the use of dimethyloxosulfonium methylide to introduce the cyclopropane ring into methyl *trans*-*o*-methylthiocinnamate. Acid-catalyzed dehydration of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1,1-dioxide gave 2-chloro-1-benzothiepin 1,1-dioxide, while reaction of *p*-toluenesulfonic acid and 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-oxide produced 1-chloronaphthalene. The latter product is explained by SO elimination from the dehydration product, 4-chloro-1-benzothiepin 1-oxide.

In a previous report[1a] we described the acid-catalyzed conversion of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin (**1**) to 2-oxo-1a,7b-dihydrocyclopropa[*c*][1]-benzothiapyran (**2**) instead of the expected 2-chloro-1-benzothiepin. A portion of the chemical evidence for **2** involved its conversion by alkali and dimethyl sulfate into *cis*-2-(methylthiophenyl)cyclopropanecarboxylic acid (**3**). Additional support for these structural



assignments is now presented with the synthesis of the *trans*-cyclopropanecarboxylic acid **10**. Also the action of acid on the sulfoxide and sulfone of **1** is reported.

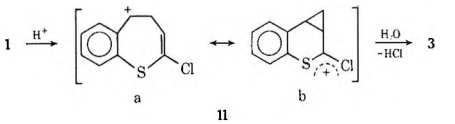
The reaction sequence outlined below[2] led to the synthesis of *trans*-2-(2-methylthiophenyl)cyclopropanecarboxylic acid (**10**). Oxidation of *o*-(methylthio)benzyl



alcohol (**6**) to *o*-(methylthio)benzaldehyde (**7**) was effected by $MnO_2$[3] (82%) or $CrO_3 \cdot 2C_5H_5N$[4] (54%) while the Doebner modification[5] of the Knoevenagel reaction (90%) was utilized in the conversion of **7** to *o*-(methylthio)cinnamic acid (**8**). The methyl ester **9** was assigned the trans configuration from the nature of the cinnamic acid synthesis and the coupling constant $J = 15$ Hz for the olefinic protons in **9**. Introduction of the cyclopropane ring utilized Corey's method[6] of methylene transfer to a cinnamic acid ester which proceeds stereoselectively to the trans-2-phenylcyclopropanecarboxylic acid ester.[7,8] The reaction of dimethyloxosulfonium methylide with **9** gave a mixture of esters which were saponified and upon fractional crystallization provided *trans*-2-(2-methylthiophenyl)-cyclopropanecarboxylic acid (**10**) in 10% overall yield.

Mohrbacher and Cromwell[9] have described a spectral method to distinguish *cis*- and *trans*-2-phenylcyclopropanecarboxylic acid; however, the uv spectral properties of **10** [$\lambda_{max}$ 252 mμ (log ε 3.94)] and **3** [$\lambda_{max}$ 253 mμ (log ε 3.94)][1] were so similar that assignment of geometric structure was not possible. In addition **10** and **3** had similar carbonyl and hydroxyl frequencies in the infrared spectra. The nmr spectra of **10** and **3** were complex and the region where the $C_1$ H (α to $CO_2H$) absorbs also contains the methyl resonance. However, the position of the $C_1$ H band is at lower field for **10** (τ 7.10–7.45) than for **3** (τ 7.45–7.92), which is similar to the $C_1$ H in *trans*- and *cis*-2-phenylcyclopropanecarboxylic acid. These data support the structural similarly of **10** and **3**; however, the strength of the stereochemical assignment resides in the synthetic origin of **10** and **3**[1] with some support from the nmr spectra. An attempt to isomerize the cis acid **3** to trans acid **10** by refluxing **3** in potassium *tert*-butoxide and *tert*-butyl alcohol for 7 days gave only starting cis acid **3**.

The proposed intermediate in the acid-catalyzed conversion of **1** to **2** is a homoallylic cation[1a] (**11**). We



were interested in observing the effect of changing the nature of the electron-donating sulfur in **1** to electron-withdrawing sulfoxide or sulfone groups on the acid-catalyzed reaction. Such electron-withdrawing groups should destabilize structures like **11b** and reduce the amount of rearrangement.

Sulfoxide **12** was obtained by oxidation of **1** with perbenzoic acid in the presence of $BF_3$ under careful temperature control (−10°). When elevated temperatures or longer reaction times are used, oxidation proceeds further to form sulfone **13**. Structural assignments for sulfoxide **12** and sulfone **13** were based on

(1) (a) For part III in this series see V. J. Traynelis and J. R. Livingston, Jr., *J. Org. Chem.*, **29**, 1092 (1964). (b) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research. (c) To whom correspondence should be sent: Department of Chemistry, West Virginia University, Morgantown, W. Va. 26506. (d) Abstracted from a portion of the Ph.D. Dissertation submitted by D. M. B. in August 1968.

(2) Preparation of compounds **5**, **6**, and **7** was accomplished independently and prior to the literature reports cited below. In each of these cases the yields reported in this work exceed those published.

(3) E. F. Pratt and J. F. van de Castle, *J. Org. Chem.*, **26**, 2973 (1961).

(4) J. R. Holum, *ibid.*, **26**, 4814 (1961).

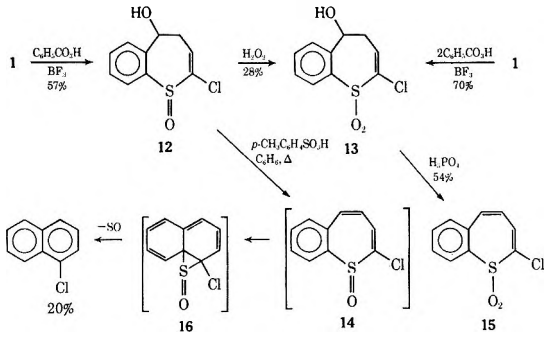
(5) O. Doebner, *Chem. Ber.*, **33**, 2140 (1900).

(6) E. J. Corey and M. Chaykovsky, *Tetrahedron Lett.*, 169 (1963). We have also observed that reaction of dimethyloxosulfonium methylide with methyl cinnamate gave a 39% yield of methyl *trans*-2-phenylcyclopropanecarboxylate.

(7) S. R. Landor and N. Punja, *J. Chem. Soc. C*, 2495 (1967).

(8) C. Kaiser, B. M. Trost, J. Beeson, and W. Weinstock, *J. Org. Chem.*, **30**, 3972 (1965).

(9) R. J. Mohrbacher and N. H. Cromwell, *J. Amer. Chem. Soc.*, **79**, 401 (1957).



elemental analysis, characteristic SO and $SO_2$ peaks in the ir, and their unique nmr spectra. Furthermore, the oxidation of sulfoxide **12** to sulfone **13** link these systems structurally.

When sulfoxide **12** was refluxed in benzene with a small amount of *p*-toluenesulfonic acid for 7 hr, 1-chloronaphthalene was isolated in 20% yield as the only identifiable product. An attractive explanation for the origin of 1-chloronaphthalene involves dehydration of **12** to 2-chloro-1-benzothiepin 1-oxide (**14**) which, after valence bond tautomerism to **16**, undergoes SO elimination. Thiirane 1-oxides[10] are known to thermally extrude SO, as are other heterocyclic systems;[11,12] however, of the thiepin sulfoxides known, thieno[3,4-*d*]thiepin 6-oxide[13] appears to be unstable (however, no mention of SO elimination) while dibenzo-[*b*,*f*]thiepin 5-oxide and its derivatives[14] did not extrude SO. Conversion of a dibenzothiazepinium salt to a phenanthridizinium salt by action of hydrogen peroxide has been explained by sulfoxide formation followed by SO extrusion.[15] An alternative pathway to 1-chloronaphthalene may involve disproportionation of **14** to 2-chloro-1-benzothiepin (known to extrude sulfur readily[16]) and 2-chloro-1-benzothiepin 1,1-dioxide (**15**); however, the absence of **15** in the product mixture precludes this pathway. The chemistry of thiepin sulfoxides is under investigation.

Sulfone **13** requires 92% phosphoric acid at 120–140° for 1 hr in order for dehydration to occur, giving the stable 2-chloro-1-benzothiepin 1,1-dioxide (**15**). The ir spectrum of **15** showed the absence of the hydroxyl group and the presence of the sulfone function, while the uv spectrum of **15** [$\lambda_{max}$ 293 mμ (log ε 4.00), 239 (4.10)] was similar to that of 1-benzothiepin 1,1-dioxide [$\lambda_{max}$ 290 mμ (log ε 3.99), 234 (4.13)].[17] The strong absorption of 1-benzothiepin 1,1-dioxide at 234 mμ was attributed to the new conjugated system[17] which resembled 3-benzothiepin 3,3-dioxide [$\lambda_{max}$ 232 mμ (log ε 4.5)][18] and the absorption maximum for **15** at 239 mμ exhibited the expected bathochromic shift. The nmr spectrum of **15** in $CDCl_3$ had no peaks at higher field than τ 3.46 and showed the expected spin–spin coupling for the $C_3$, $C_4$, and $C_5$ protons. These data are all consistent with the structural assignment for **15**.

A comparison of the acid-catalyzed dehydration of **1**, **12**, and **13** illustrates the influence of the electron-withdrawing sulfoxide and sulfone group, as described above, which lead to normal dehydration and no carbon skeleton rearrangement.

## Experimental Section[19]

*o*-(**Methylthio**)**benzoic Acid** (**5**).—In a modification of the procedure of Kucsman and Kremmer[20] a mixture of dimethyl sulfate (227 g, 1.80 mol) and a solution of thiosalicyclic acid (180 g, 1.17 mol) and sodium hydroxide (95.5 g, 2.39 mol) in water (720 ml) was refluxed for 6 hr and treated with sodium hydroxide (36 g, 0.90 mol) in water (100 ml) and upon work-up gave 189 g (96%) of *o*-(methylthio)benzoic acid, mp 167–169° (lit.[20] mp 170°). Recrystallization from toluene gave white needles, mp 170°.

*o*-(**Methylthio**)**benzyl Alcohol** (**6**).—The method of Grice and Owen[21] was applied to the reduction of *o*-(methylthio)benzoic acid (75.0 g, 0.446 mol) by $LiAlH_4$ (slurry, 17.0 g, 0.446 mol) in ether (500 ml). After 20 hr of reflux and an alkaline work-up, the yield of *o*-(methylthio)benzyl alcohol, bp 114° (0.7 mm), was 59 g (86%). An analytical sample, bp 155–156° (17 mm), $n^{20}D$ 1.6075 [lit.[21] bp 88° (0.001 mm), $n^{20}D$ 1.6060], was obtained after two distillations.

*Anal.* Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54. Found: C, 62.46, 62.28; H, 6.46, 6.66.

*o*-(**Methylthio**)**benzaldehyde** (**7**). **Method A.**—By application of the procedure of Pratt and van de Castle,[3] freshly prepared manganese dioxide[22] (158 g, 1.82 mol) and *o*-(methylthio)-benzyl alcohol (70.0 g, 0.455 mol) gave after distillation 56.5 g (82%) of *o*-(methylthio)benzaldehyde, bp 97–101° (0.7 mm), $n^{20}D$ 1.6338 [lit.[23] bp 149° (19 mm)]. An analytical sample, bp 80° (0.05 mm), $n^{20}D$ 1.6355, was prepared *via* the bisulfite addition product followed by distillation.

*Anal.* Calcd for $C_8H_8OS$: C, 63.13; H, 5.30. Found: C, 63.42; H, 5.31.

**Method B.**—*o*-(Methylthio)benzyl alcohol (10.6 g, 0.070 mol) in pyridine (25 ml) was oxidized by bispyridine–chromium trioxide (33.7 g, 0.213 mol) in dry pyridine (100 ml) using Holum's[4] procedure and gave 5.7 g (54%) of *o*-(methylthio)benzaldehyde, bp 119–122° (3.8 mm), $n^{20}D$ 1.6308.

*trans-o*-(**Methylthio**)**cinnamic Acid** (**8**).—*o*-(Methylthio)benzaldehyde (12.9 g, 0.085 mol), malonic acid (19.4 g, 0.186 mol), piperidine (0.75 ml), and pyridine (30 ml) were heated in an oil bath at 80° for 1 hr, after which the temperature was increased to 100° for 2 hr and the solution was finally refluxed for 0.5 hr.[5] The solution was cooled, poured onto 12% hydrochloric acid and ice, filtered, and washed with water. The dry solid was recrystallized from toluene and gave 14.8 g (90%) of *trans-o*-(methylthio)cinnamic acid, mp 175–176° (lit.[24] mp 176°).

**Methyl** *trans-o*-(**Methylthio**)**cinnamate** (**9**).—A solution of *trans-o*-(methylthio)cinnamic acid (14.8 g, 0.076 mol) in methanol (160 ml) and concentrated sulfuric acid (6 ml) was refluxed for 6 hr. After the solution was concentrated, diluted with water, and extracted with ether, the ether extract was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and distilled. The ester was collected as a light green oil, bp 119–123° (0.5 mm), yield 14.0 g (89%), which crystallized on standing. Two recrystallizations from Skelly B gave pure methyl *trans-o*-(methylthio)cinnamate: mp 43–44°; nmr ($CCl_4$) τ 1.93 (d, 1, $J$ = 15 Hz, ArHC=CHCO$_2$CH$_3$), 2.80 (m, 4, aromatic H), 3.74 (d, 1, $J$ = 15 Hz, ArHC=CHCO$_2$CH$_3$), 6.18 (s, 3, $OCH_3$), 7.64 (s, 3, $SCH_3$).

(10) G. E. Hartzell and J. N. Paige, *J. Amer. Chem. Soc.*, **88**, 2616 (1966).
(11) H. H. Szmant and L. M. Alfonso, *ibid.*, **79**, 205 (1957).
(12) R. H. B. Galt, J. D. Loudon, and A. D. B. Sloan, *J. Chem. Soc.*, 1588 (1958).
(13) R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 3017 (1968).
(14) A. Trifunac and E. T. Kaiser, *J. Phys. Chem.*, **74**, 2236 (1970).
(15) C. K. Bradsher and J. W. McDonald, *J. Org. Chem.*, **27**, 4475 (1962).
(16) V. J. Traynelis, J. R. Livingston, and Y. Yoshikawa, unpublished observations.
(17) V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).
(18) W. E. Truce and F. J. Lotspeich, *J. Amer. Chem. Soc.*, **78**, 848 (1956).

(19) All melting points and boiling points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., or Schwartzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were determined on a Perkin-Elmer Infracord, ultraviolet spectra were measured on a Bausch and Lomb Spectronic 505 spectrometer, and the nmr spectra were obtained on a Varian Associates 60-MHz nmr spectrometer.
(20) A. Kucsman and T. Kremmer, *Acta Chim. Acad. Sci. Hung.*, **34**, 75 (1962).
(21) R. Grice and L. Owen, *J. Chem. Soc.*, 1947 (1963).
(22) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *ibid.*, 1094 (1952).
(23) B. Eistert, W. Schade, and H. Selzer, *Chem. Ber.*, **97**, 1470 (1964).
(24) C. Chmelewsky and P. Friedlander, *ibid.*, **46**, 1903 (1913).

*Anal.* Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.83, 63.62; H, 5.93, 5.78.

*trans*-2-(2-Methylthiophenyl)cyclopropanecarboxylic Acid (10). —Trimethyloxosulfonium iodide (14.1 g, 0.064 mol) was added to a stirred slurry of sodium hydride (0.064 mol) in dimethyl sulfoxide (50 ml) under nitrogen and stirred for 15 min. Methyl *trans*-*o*-(methylthio)cinnamate (12 g, 0.058 mol) in dimethyl sulfoxide (20 ml) was added to this mixture at a temperature below 50° and the resulting mixture was heated for 2.5 hr, poured into water, and extracted with $CHCl_3$. After the $CHCl_3$ extract was washed with $H_2O$ and dried ($MgSO_4$) and the solvent was removed, the residue was distilled and gave 1.5 g of crude ester, bp 131–135° (0.55 mm). The crude ester and potassium hydroxide (1.5 g, 0.038 mol) were dissolved in 50% aqueous methanol and refluxed for 2 hr, after which acidification and filtration gave 1.2 g (10% overall yield) of *trans*-2-(2-methylthiophenyl)cyclopropanecarboxylic acid, mp 111–114°. An analytical sample was prepared by crystallization from benzene–Skelly B and had the following constants: mp 115–116°; uv max (95% $C_2H_5OH$) 252 mμ (log ε 3.94); ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) τ 2.88 (m, 4, aromatic H), 7.25 (m, 1), 7.62 (s, 3, $SCH_3$), 8.31 (m, 3).

*Anal.* Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.54; H, 5.82.

Attempted Isomerization of *cis*-2-(2-Methylthiophenyl)cyclopropanecarboxylic Acid (3).—A solution of *cis*-2-(2-methylthiophenyl)cyclopropanecarboxylic acid[1a] (100 mg, 0.56 mmol) in 20 ml of 0.1 *N* potassium *tert*-butoxide in *tert*-butyl alcohol was refluxed for 1 week. The solution was acidified, diluted with water, and extracted with $CHCl_3$. When the $CHCl_3$ was removed, 60 mg (60%) of starting acid, mp 166–167° (lit.[1a] mp 168–169°), was recovered.

2-Chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-Oxide (12). —To a solution of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin (2.38 g, 0.011 mol), prepared as described previously,[1a] and boron trifluoride etherate (2.34 g, 0.011 mol) in anhydrous ether (100 ml) was added a solution of perbenzoic acid (0.15 mol) in anhydrous ether while the temperature was maintained below −10°. After 3 hr at this temperature, the solution was allowed to warm up to room temperature and treated with sodium carbonate solution and the ether layer was separated. The aqueous layer was extracted with $CHCl_3$, the combined $CHCl_3$ and ether solution was dried ($MgSO_4$), and the solvent was removed to give 1.46 g (57%) of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-oxide as a viscous oil. The oil slowly solidified and crystallization from toluene gave an analytical sample: mp 141–142° dec; uv max (95% $C_2H_5OH$) 255 mμ (log ε 3.53), inflection 230 (3.79); ir (Nujol mull) 3310 (COH) and 1030 $cm^{-1}$ (>S=O); nmr ($CF_3CO_2H$) τ 2.12 (m, 4, aromatic H), 3.37 (d, 1, $J_{C_5-C_{4a}}$ = 6 Hz, $C_5$ H), 3.50 (dd, 1, $J_{C_3-C_{4b}}$ = 6, $J_{C_3-C_{4a}}$ = 3 Hz, $C_3$ H), 6.40 (two dd, 1, $J_{C_{4a}-C_{4b}}$ = 20, $J_{C_{4a}-C_5}$ = 6, $J_{C_{4a}-C_3}$ = 3 Hz, $C_{4a}$ H), 7.28 (dd, 1, $J_{C_{4b}-C_{4a}}$ = 20, $J_{C_{4b}-C_3}$ = 6 Hz, $C_{4b}$ H).

*Anal.* Calcd for $C_{10}H_9ClO_2S$: C, 52.52; H, 3.97. Found: C, 52.74; H, 3.80.

2-Chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1,1-Dioxide (13). Method A.—A solution of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin (4.24 g, 0.020 mol), perbenzoic acid (0.044 mol), and boron trifluoride etherate (6 ml) in ether (130 ml) was allowed to stand overnight, the ether was removed, and the residue was treated with 10% sodium hydroxide solution. The resulting precipitate was filtered, dried, and recrystallized from benzene–hexane (after Norit treatment) to give 3.2 g (70%) of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1,1-dioxide: mp 117.5–119°; uv max (95% $C_2H_5OH$) 237 mμ (log ε 3.74), 270 (3.74), 278 (3.71); ir (Nujol mull) 3310 (COH) and 1320, 1170 $cm^{-1}$ (>S(O)O); nmr ($CDCl_3$) τ 2.2 (m, 4, aromatic H), 3.62 (dd, 1, $J_{5-4a}$ = 6, $J_{5-4b}$ = 4.5 Hz, $C_5$ H), 3.88 (dd, 1, $J_{3-4a}$ = 4.5, $J_{3-4b}$ = 11.5 Hz, $C_3$ H), 6.61 (s, 1, OH), 6.94 (two dd, 1, $J_{4a-4b}$ = 20, $J_{4a-5}$ = 6, $J_{4a-3}$ = 4.5 Hz, $C_{4a}$ H), 7.61 (two dd, 1, $J_{4a-4b}$ = 20, $J_{4b-5}$ = 4.5, $J_{4b-3}$ = 11.5 Hz, $C_{4b}$ H).

*Anal.* Calcd for $C_{10}H_9ClO_3S$: C, 49.09; H, 3.71. Found: C, 49.66; H, 3.85.

Method B.—A solution of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-oxide (500 mg, 2.2 mmol), 30% hydrogen peroxide (2.5 ml), and acetone (10 ml) was refluxed for 3.5 hr, diluted with water, and extracted with ether. After the ether extract was dried and the solvent was removed, the residue was crystallized from benzene and gave 130 mg (28%) of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1,1-dioxide, mp 110–116°. Recrystallization from benzene–hexane gave pure sulfone, mp 116–117°.

2-Chloro-1-benzothiepin 1,1-Dioxide (15).—2-Chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1,1-dioxide (1.00 g, 0.0041 mol) was added to 92% phosphoric acid prepared by dissolving phosphorus pentoxide (5.0 g) in 85% phosphoric acid (20 ml) and the solution was heated on a steam bath for 30 min and then at 115–143° for 60 min. The reaction mixture was poured onto ice and the solid was filtered and dried to give 0.50 g (54%) of 2-chloro-1-benzothiepin 1,1-dioxide, mp 136–136.5°. Recrystallization from benzene gave an analytical sample: mp 137–138°; uv inflection (95% $C_2H_5OH$) 223 mμ (log ε 4.38), 239 (4.10); uv max 293 mμ (log ε 4.00); ir (Nujol mull) 1310 and 1030 $cm^{-1}$ (>S(O)O); nmr ($CF_3CO_2H$) τ 1.80 (m, 1, $ArC_9$ H), 2.27 (m, 3, ArH), 2.44 (d, 1, $J$ = 12.5 Hz, $C_5$ H), 2.83 (d, 1, $J$ = 7.5 Hz, $C_3$ H), 3.29 (dd, 1, $J_{C_4-C_3}$ = 7.5, $J_{C_4-C_5}$ = 12.5 Hz, $C_4$ H).

*Anal.* Calcd for $C_{10}H_7ClO_2S$: C, 52.98; H, 3.11. Found: C, 53.24; H, 3.13.

Reaction of 2-Chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-Oxide and Acid.—A mixture of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-oxide (1.00 g, 0.0044 mol), a few crystals of *p*-toluenesulfonic acid monohydrate, and benzene (50 ml) was refluxed for 7 hr under nitrogen. The solution was cooled and concentrated and the residue was poured onto a column of silica gel (50 g). Elution with Skelly B gave 0.14 g (20%) of 1-chloronaphthalene in fractions 2 and 3. The infrared spectrum of this sample was identical with that of an authentic sample and a mixture melting point of the picrate, mp 129–131°, of the reaction product 1-chloronaphthalene and an authentic sample was not depressed.

Attempted dehydration of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin 1-oxide with phosphorus pentoxide in benzene gave only recovered starting material (80%).

**Registry No.**—**6**, 33384-77-9; **7**, 7022-45-9; **9**, 36287-17-9; **10**, 36287-18-0; **12**, 36287-19-1; **13**, 36287-20-4; **15**, 36287-21-5.

# 5-Substituted Bicyclo[2.1.1]hexenes[1]

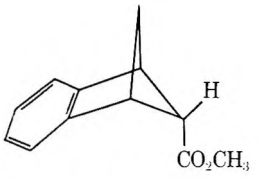
Kenneth B. Wiberg* and Richard W. Ubersax[2]

*Department of Chemistry, Yale University, New Haven, Connecticut 06520*

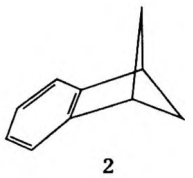
*Received March 27, 1972*

The synthesis of 5-substituted bicyclo[2.1.1]hexenes *via* the dehalogenation of 2,3-dichlorobicyclo[2.1.1]-hexanes is described. The reaction was successful when the 5 substituent was carbethoxy, hydroxymethyl, or 2-hydroxyethyl. However, it failed when the substituent was acetoxy, and only benzene, derived from rearrangement and elimination of acetic acid, was obtained. The nmr spectra of the bicyclo[2.1.1]hexenes and of the 2,3-dichlorobicyclo[2.1.1]hexanes are discussed.

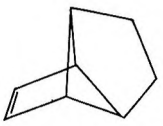
Bicyclo[2.1.1]hexene derivatives are of interest in connection with studies of double bond participation and of thermal rearrangements. The preparation of some of these compounds has been difficult,[3] although methyl benzobicyclo[2.1.1]hexene-1-carboxylate (**1**),[4] benzobicyclo[2.1.1]hexene (**2**),[5] tricyclo[3.3.0.0$^{2,6}$]oct-3-ene (**3**),[6] *exo*-bicyclo[2.1.1]hex-2-en-5-yl acetate (**4**),[7] and the parent hydrocarbon[8] have been reported. The



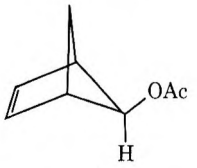

**1**



**2**



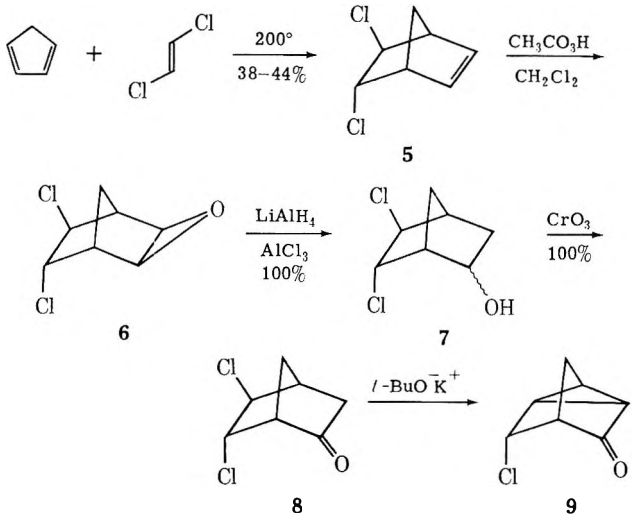
**3**




**4**

synthetic methods employed for these compounds were not suited to the preparation of the 5-substituted derivatives of particular interest to us. The following will report convenient preparations for some of these compounds.

The Diels–Alder reaction of *trans*-1,2-dichloroethylene with cyclopentadiene gave *trans*-5,6-dichloronorbornene (**5**).[9] Epoxidation with peracetic acid afforded *exo*-2,3-epoxy-*trans*-5,6-dichloronorbornane (**6**).[10] Reduction with lithium aluminum hydride–aluminum chloride to the alcohol **7** followed by oxidation with chromic acid gave the ketone **8**. The arrangement of the chlorines in **8** was indicated by its facile reaction with potassium *tert*-butoxide to give *endo*-5-chlorotricyclo[2.2.1.0$^{2,6}$]heptan-3-one (**9**). Only an exo chlorine would be expected to be displaced under the reaction conditions.




Selenium dioxide oxidation of **8** gave the diketone **10**, which was converted to its monotosylhydrazone. The latter, when passed over basic alumina,[11] gave the yellow crystalline diazo ketone **11**. Photolysis of **11** in methanol gave a mixture of methyl *endo*- and *exo*-*trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-carboxylates in an 85:15 ratio. Saponification with methanolic potassium hydroxide gave a 50:50 mixture of the epimeric acids **13** and **14**, which could be separated by recrystallization from carbon tetrachloride.

The esters **12** were readily reduced to the corresponding carbinols **15** and **16** with lithium aluminum hydride. Elimination of halogen from **12**, **15**, and **16** proved difficult. Magnesium turnings in ether both with and without magnesium iodide, zinc dust in ethanol, the zinc–copper couple, and chromous sulfate in aqueous dimethylformamide[12] all failed to give any significant eliminations. Magnesium amalgam in glyme led to a slow elimination of halogen. However, the disodium phenanthrene[13] was found to effect dehalogenation very effectively at low temperature. Catalytic hydrogenation of **17** and **18** gave the corresponding bicyclo[2.1.1]hexane derivatives, as shown by comparison of nmr and ir spectra with those of authentic samples.[14]

The acid **13** was subjected to the Arndt–Eistert reaction followed by reduction and dehalogenation to give 2-(bicyclo[2.1.1]hexen-*endo*-5-yl)ethanol (**19**). The acetate derived from **19** reacted with diazomethane

(1) This investigation was supported by Public Health Service Grant No. 12800 from the National Institutes of General Medical Science. A preliminary report of part of this work has appeared: K. B. Wiberg and R. W. Ubersax, *Tetrahedron Lett.*, 3063 (1968).

(2) Taken in part from the Ph.D. thesis of R. W. U., 1969.

(3) J. Meinwald and J. K. Crandall, *J. Amer. Chem. Soc.*, **88**, 1292 (1966).

(4) H. Tanida and Y. Hata, *ibid.*, **88**, 4289 (1966).

(5) M. Pomerantz, *ibid.*, **88**, 5349 (1966).

(6) J. Meinwald and B. E. Kaplan, *ibid.*, **89**, 2611 (1967).

(7) S. Masamune, E. N. Cain, R. Vukov, S. Takada, and N. Nakatsuka, *Chem. Commun.*, 243 (1969).

(8) J. Meinwald and F. Uno, *J. Amer. Chem. Soc.*, **90**, 800 (1968); F. T. Bond and L. Scerbo, *Tetrahedron Lett.*, 2789 (1968).

(9) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **78**, 2819 (1956).

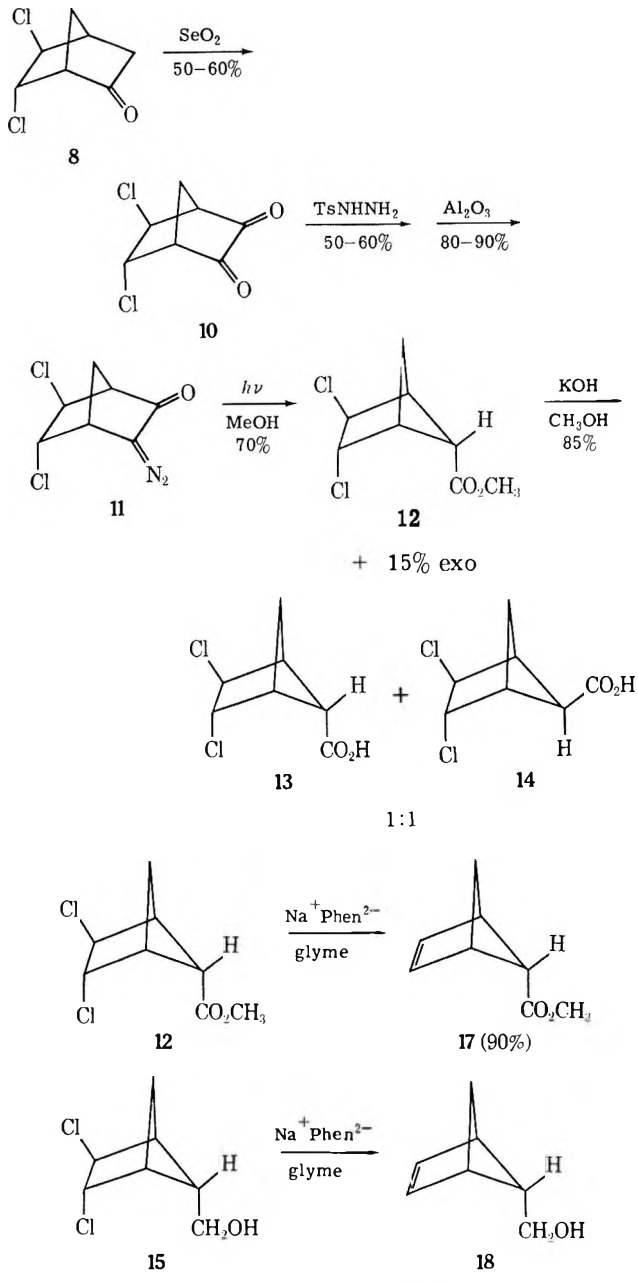
(10) V. Mark, U. S. Patent 2,771,470 (Nov 20, 1956); *Chem. Abstr.*, **51**, 6686 (1957).

(11) The procedure of Meinwald and Crandall[1] was used.

(12) W. C. Kray and C. E. Castro, *J. Amer. Chem. Soc.*, **86**, 4603 (1964).

(13) E. Vogel, H. Kiefer, and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **3**, 442 (1964). *Cf.* R. N. McDonald and D. G. Frickey, *J. Amer. Chem. Soc.*, **90**, 5316 (1968); L. A. Paquette and J. C. Stowell, *Tetrahedron Lett.*, 4159 (1969).

(14) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Amer. Chem. Soc.*, **83**, 3998 (1961).




and cuprous bromide to give 2-(*anti*-tricyclo[3.1.1.$0^{2,4}$]-hept-*endo*-6-yl)ethyl acetate, which was reduced to the corresponding alcohol **20** with lithium aluminum hydride. The configuration of the cyclopropane group is that expected for addition to the least hindered side of the double bond.[15] It is shown to occupy the assigned position by its nmr spectrum (Table I). The chemical shifts of protons a and b are unaffected by the cyclopropane ring, whereas protons e and f show large diamagnetic shifts, indicating that they lie over the cyclopropane ring.[16]

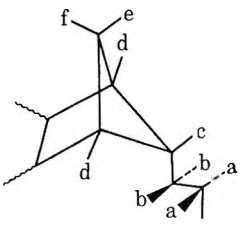
The preparation of *endo*-bicyclo[2.1.1]hexen-5-ol also was attempted. The endo acid **13** was converted to the methyl ketone **21** *via* the acid chloride and treatment with dimethylzinc in pentane. Treatment of **21** with either *m*-chloroperbenzoic acid or buffered trifluoroacetic acid was unsuccessful, only unreacted ketone being recovered. However, the reaction did

(15) A. C. Cope, S. Moon, and P. E. Peterson, *J. Amer. Chem. Soc.*, **84**, 1935 (1962).

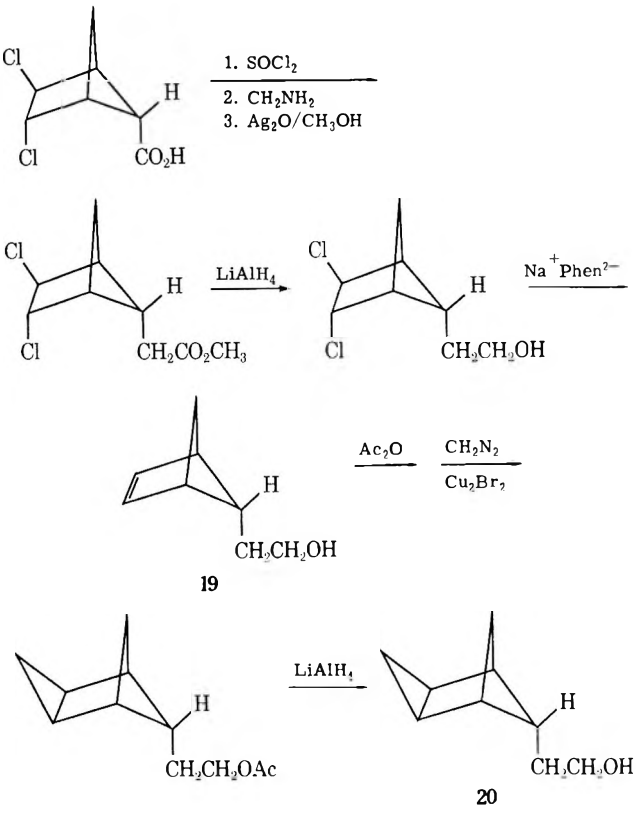
(16) *Cf.* C. D. Poulter, R. S. Boikess, J. I. Brauman, and S. Winstein, *ibid.*, **94**, 2291 (1972).

TABLE I

NMR SPECTRA OF 2-(BICYCLO[2.1.1]HEXEN-*endo*-5-YL)ETHANOL (**19**) AND 2-(*anti*-TRICYCLO[3.1.1.$0^{2,4}$]HEPT-*endo*-6-YL)ETHANOL (**20**)

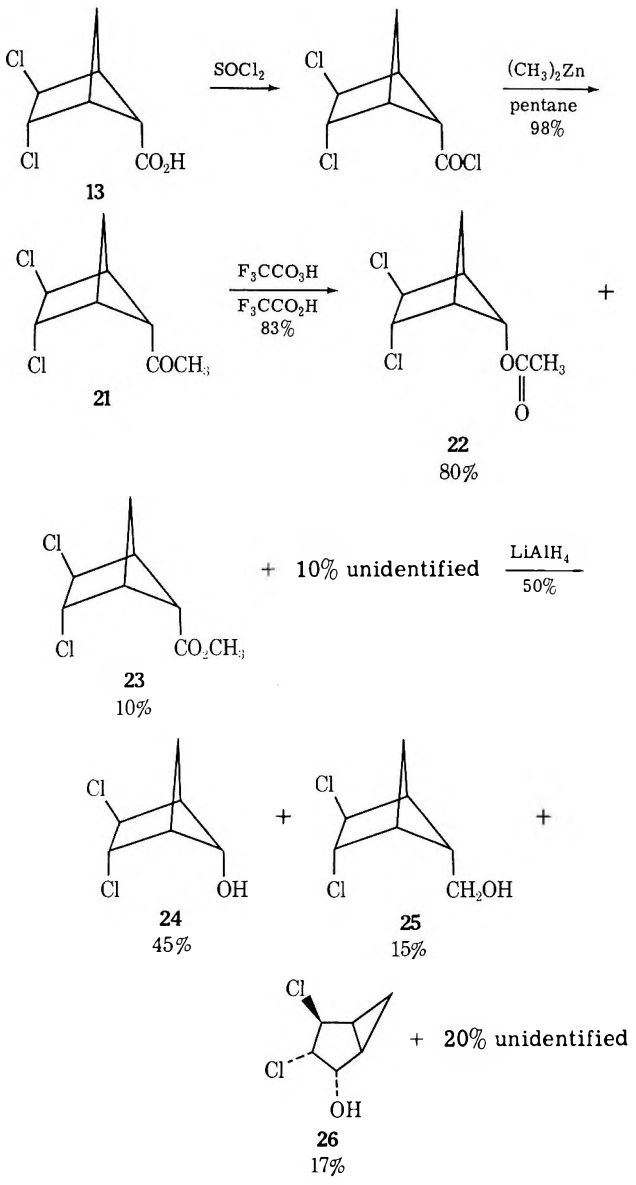



| Proton | Chemical shift, ppm 19 | 20 |
|---|---|---|
| a | 6.57 | 6.54 |
| b | 8.42 | 8.40 |
| c | 6.78 | 7.62 |
| d | 7.50 | 7.79 |
| e | 7.68 | 8.42 |
| f | 7.68 | 9.00 |

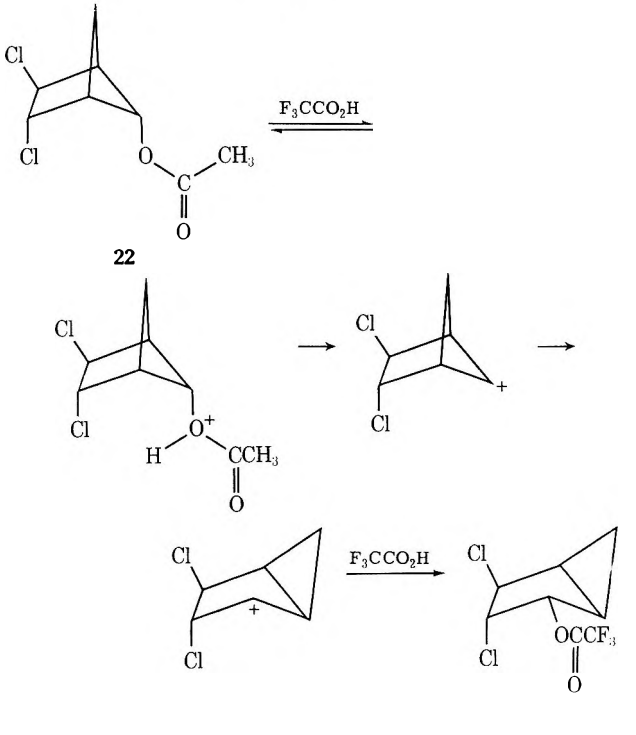



proceed using unbuffered trifluoroperacetic acid in the presence of trifluoroacetic acid as a catalyst, giving the acetate along with some methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-carboxylate formed by methyl migration, and some unidentified material. Reduction of the above mixture with lithium aluminum hydride gave a mixture of alcohols in 50% yield. The products were *trans*-2,3-dichlorobicyclo[2.1.1]-hexan-*endo*-5-ol (**24**) (45%), *trans*-2,3-dichlorobicyclo-[2.1.1]hexane-*endo*-5-methanol (**25**) (15%), *cis*-2-chloro-*trans*-3-chloro-*trans*-4-hydroxybicyclo[3.1.0]hexane (**26**) (17%), and an unidentified product (20%) which had a vpc retention time about twice that of the other compounds.

The carbinol **25** is derived from **23**. The alcohol **26** could arise from an acetate formed in the Baeyer–Villiger reaction as shown in Scheme I.

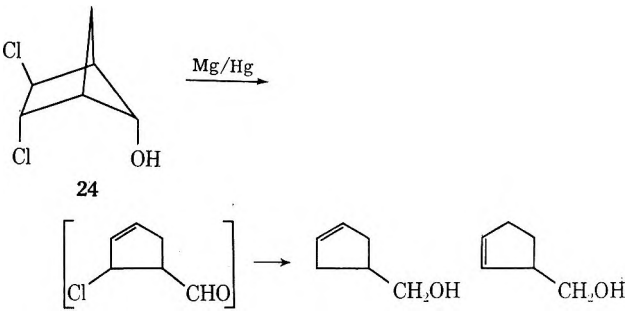


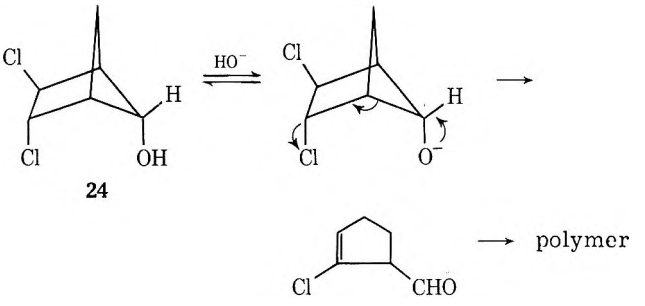

Scheme I



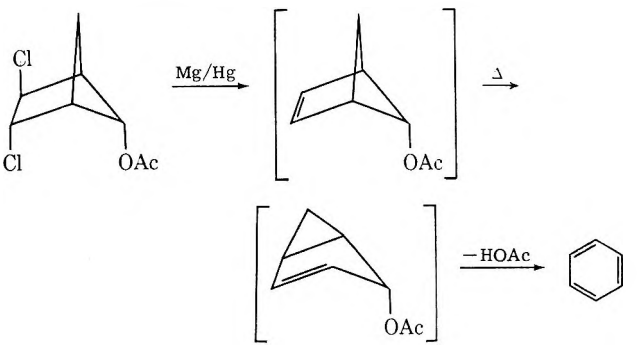

The use of methyllithium for the conversion of the acetates to alcohols raised the yield to 67%.

Conversion of *trans*-2,3-dichlorobicyclo[2.1.1]hexan-*endo*-5-ol to bicyclo[2.1.1]hexen-*endo*-5-ol with either magnesium amalgam or sodium phenanthrene was unsuccessful. The major product resulting from the magnesium amalgam reaction was $\Delta^3$-cyclopentenylmethanol along with a small amount of $\Delta^2$-cyclopentenylmethanol. 2-Chloro-$\Delta^3$-cyclopentenecarboxaldehyde is probably an intermediate in the reaction. The formation of this compound under basic conditions would be followed by dehydrohalogenation, giving cyclopentadienecarboxaldehyde, which could lead to the polymeric material found in the aqueous base hydrolysis of **22**.




Dehalogenation of the acetate **22** would be expected to eliminate the undesirable cleavage reaction. However, the reaction of **22** with magnesium amalgam gave only benzene. This is not unexpected, since bicyclo[2.1.1]hexene rearranges thermally to bicyclo[3.1.0]hexene at 140°.[17] The reaction conditions for the magnesium amalgam reaction (95°) could lead to a similar rearrangement.[18] The bicyclo[3.1.0]hexenyl

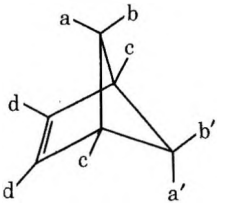



(17) F. T. Bond and L. Scerbo, *Tetrahedron Lett.*, 2789 (1968).

(18) The rearrangement of *exo*-bicyclo[2.1.1]hex-2-en-5-yl acetate to *exo*-bicyclo[3.1.0]hex-2-en-6-yl acetate occurs readily at 85°: S. Masamune, S. Takada, N. Nakatsuka, R. Vukov, and E. N. Cain, *J. Amer. Chem. Soc.*, **91**, 4322 (1969).

TABLE II

NMR SPECTRA OF BICYCLO[2.1.1]HEXENE DERIVATIVES ($\tau$)[a]

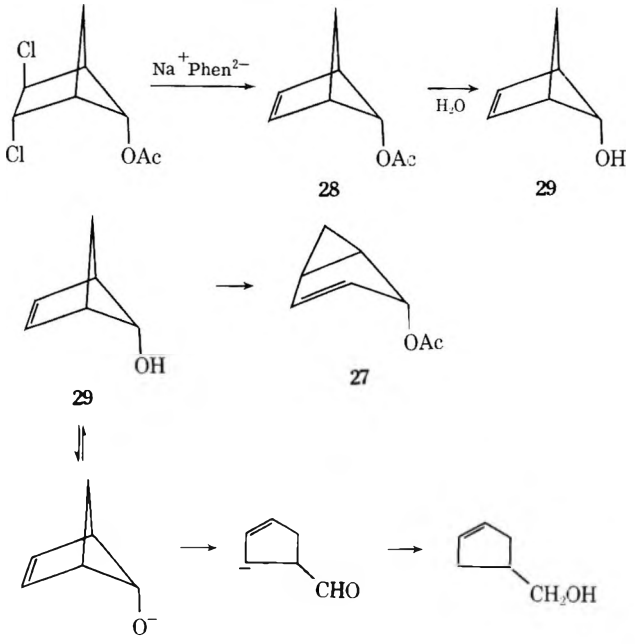



| Registry no. | Compd | a | b | a'(b') | c | d | Others | |
|---|---|---|---|---|---|---|---|---|
| 35672-56-1 | *endo*-$CO_2CH_3$ | 7.80 (d) ($J$ = 6 Hz) | 7.58 (dt) | 6.40 (m) | 7.12 (p) ($J$ = 2 Hz) | 3.18 (t) ($J$ = 2 Hz) | $CO_2CH_3$ | 6.40 (s) |
| 20441-30-9 | *endo*-$CH_2OH$ | 7.70 (m) | 7.70 (m) | 6.75 (tt) | 7.50 (m) | 3.42 ($J$ = 2 Hz) | $CH_2O$, OH | 6.55 (m) 7.21 (s) |
| 35672-58-3 | *endo*-$CH_2OAc$ | 7.65 (m) | 7.65 (m) | 6.78 (tt) ($J$ = 7, 2 Hz) | 7.45 (m) | 3.35 (t) ($J$ = 2 Hz) | $CH_2O$ $CH_3CO$ | 6.04 (d) ($J$ = 7 Hz) 8.08 (s) |
| 35672-59-4 | *endo*-$CH_2CH_2OH$ | 7.68 (m) | 7.68 (m) | 6.78 (tt) | 7.50 (m) | 3.30 (t) ($J$ = 2 Hz) | $CH_2O$ $CH_2CH_2O$ OH | 6.57 (t) ($J$ = 7 Hz) 8.42 (t) ($J$ = 7 Hz) 6.55 (s) |
| 20441-31-0 | *exo*-$CH_2OH$ | 7.78 (t) | 7.10 (m) | 7.10 (m) | 7.57 (g) | 3.10 (t) ($J$ = 2 Hz) | $CH_2O$ OH | 6.16 (d) ($J$ = 8 Hz) 6.82 (s) |

[a] The spectra were determined at 60 MHz using carbon tetrachloride as the solvent.

acetate would be expected readily to be converted to benzene by elimination of acetic acid.[19]

The sodium phenanthrene reaction carried out at −40° supports the formation of a bicyclo[3.1.0]hexene intermediate. The products were bicyclo[3.1.0]-hex-2-en-3-ol (**27**) and $\Delta^3$-cyclopentenylmethanol. These products could be formed as follows.[20]




The acetate **28** is probably formed, but may readily be hydrolyzed during work-up. Thermal rearrangement of the alcohol **29** would give the observed bicyclohexenol **27**. Rearrangement of the anion derived from **29** would give the cyclohexenecarboxaldehyde, which could be reduced to cyclopentenylmethanol under the reaction conditions.

**Nmr Spectra of 5-Substituted Bicyclo[2.1.1]hexenes.**—The nmr spectra of the 5-substituted bicyclo[2.1.1]-hexenes are somewhat simpler than those of the corresponding bicyclo[2.1.1]hexanes.[21] Because of the similar geometries of the two ring systems, the coupling constants of the methylene protons are essentially the same.

The distinct feature of the spectra of the bicyclo-[2.1.1]hexenes is the sharp triplet of the olefinic protons which are coupled to the adjacent bridgehead proton ($J$ = 2 Hz) and are apparently coupled to the distant bridgehead proton ($J$ = 1.5 Hz). This is similar to the coupling found for the other bicyclo[2.1.1]hexenes.[22] The chemical shifts and description of the proton absorptions of selected bicyclo[2.1.1]hexenes are listed in Table II.

The carbinyl protons of bicyclo[2.1.1]hexene-*endo*-5-methanol appear as an unsymmetrical multiplet rather than as a sharp doublet as found with the exo isomer. However, in both the corresponding acetate and tosylate, the carbinyl protons do appear as a doublet. The unsymmetrical pattern found in the endo methanol appear to be related to the hydroxy group, but the details remain unclear.

**Nmr Spectra of *trans*-2,3-Dichlorobicyclo[2.1.1]-hexanes.**—The spectra of a group of *trans*-2,3-dichlorobicyclo[2.1.1]hexanes are summarized in Table III. In all of the endo-substituted derivatives, the C-6 methylene protons appear as a characteristic multiplet between $\tau$ 8.15 and 8.50. In addition, the endo C-3 proton always appears at lower field than the exo C-2 proton. One would expect these protons to have substantially different chemical shifts due to the magnetic anisotropy of the 5 substituent.

In the case of the exo 5-substituted derivatives, the C-2 and C-3 protons appear as a broad singlet between $\tau$ 5.65 and 5.75. These protons are expected to have about the same chemical shift, since the 5 substituent is now approximately equidistant from the protons in question.

The $CH_3CH_2$ protons of ethyl *trans*-2,3-dichloro-

(19) The bicyclo[3.1.0]hex-2-en-6-yl acetates are stable thermally[18] but would not be expected to be stable in the presence of magnesium chloride under the reaction conditions.

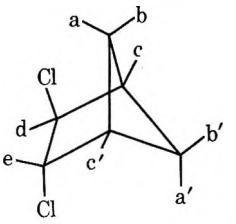
(20) Masamune, *et al.*,[18] have reported that the hydrolysis of *exo*-bicyclo-[2.1.1]hex-2-en-5-yl acetate gives $\Delta^3$-cyclopentenecarboxaldehyde as one of the products.

(21) K. B. Wiberg and B. R. Lowry, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(22) K. E. Wilzbach, J. S. Ritscher, and L. Kaplan, *ibid.*, **89**, 1031 (1967); J. Meinwald and B. E. Kaplan, *ibid.*, **89**, 2611 (1967).

Table III

Nmr Spectra of *trans*-2,3-Dichlorobicyclo[2.1.1]hexane Derivatives ($\tau$)[a]




| Registry no. | Compd | a,b | a′(b′) | c(c′) | d | e | Other | |
|---|---|---|---|---|---|---|---|---|
| 35672-61-8 | $CO_2CH_3$[b] | 8.05–8.50 (m) | 6.75–7.15 (m) | | 5.15 (m) | 5.68 (m) | $OCH_3$ | 6.32 (s) |
| 55672-62-9 | $CO_2H$[b] | 8.30 (m) | 6.80 (m) | 7.07 (m) | 5.15 (m) | 5.73 (m) | $CO_2H$ | −1.55 (r) |
| 35672-63-0 | $CH_2OH$[b] | 8.35 (m) | 7.63 (t) | 7.18 (m) | 5.54 (m) | 5.72 (m) | $CH_2OH$ | 6.30 (d) |
| | | | | | | | OH | 6.57 (s) |
| 35908-76-0 | COCl[b] | 8.23 (m) | 6.75–7.05 (m) | 6.37–6.75 (m) | 5.22 (m) | 5.60 (m) | | |
| 35672-64-1 | $COCHN_2$[b] | 8.33 (m) | 6.67–7.13 (m) | | 5.05 (m) | 5.80 (m) | $CHN_2$ | 4.70 (s) |
| 55672-65-2 | $CH_2CO_2CH_3$[b] | 8.30 (m) | 7.42 (s) | 7.20 (m) | 5.57 (m) | 5.72 (m) | $OCH_3$ | 6.34 (s) |
| | | | | | | | $CH_2CO_2$ | 7.42 (s) |
| 35672-66-3 | $CH_2CH_2OH$[b] | 8.42 (m) | 7.75 (m) | 7.25 (m) | 5.50 (m) | 5.72 (m) | $CH_2CH_2O$ | 8.28 (q) |
| | | | | | | | $CH_2CH_2O$ | 6.45 (t) |
| | | | | | | | OH | 6.13 (s) |
| 35672-68-5 | $COCH_3$[b] | 8.37 | 6.75 (m) | 6.93–7.35 (m) | 5.35 (m) | 5.80 (m) | $COCH_3$ | 7.91 (s) |
| 35672-67-4 | $COCH_2CH_3$[b] | 8.10–8.50 (m) | 6.67 (m) | 6.98–7.30 (m) | 5.24 (m) | 5.72 (m) | $CH_3CH_2$ | 5.72 (p) |
| | | | | | | | $CH_3$ | 9.00 (t) |
| 35672-69-6 | OAc[b] | 8.46 (m) | 5.37 (q) | 7.00 (m) | 5.49 (m) | 5.75 (m) | $COCH_3$ | 7.98 (r) |
| 35672-70-9 | OH[b] | 8.50–9.03 (m) | 6.01 (q) | 7.18 (t) | 5.49 (m) | 5.74 (m) | OH | 7.87 (s) |
| 35672-71-0 | $CO_2CH_3$[b] | 8.20 (t) | 7.10 (d) | 7.45 (m) | 6.93–7.10 (m) | 5.66 (m) | $OCH_3$ | 6.20 (s) |
| 35672-72-0 | $CO_2H$[b] | 8.20 (t) | 6.92–7.13 (m) | 7.44 (d) | 6.92–7.13 (m) | 5.72 (m) | $CO_2H$ | −1.50 (s) |
| 35672-73-2 | $CH_2OH$[c] | 8.29 (t) | 7.35–7.92 (m) | | | 5.75 (m) | OH | 6.45 (s) |

[a] The spectra were determined at 60 MHz using carbon tetrachloride as the solvent. [b] Endo isomer. [c] Exo isomer.

bicyclo[2.1.1]hexyl-*endo*-5 ketone appear as a symmetrical pentet centered at $\tau$ 7.52. Irradiation at the methyl frequency reduced the pattern to an AB quartet ($J$ = 7 Hz, $\delta$ 13 Hz). The methylene hydrogens are diastereotopic, and as a result are magnetically nonequivalent.

## Experimental Section

*trans*-5,6-Dichloro-*exo*-2-hydroxybicyclo[2.2.1]heptane.—Into a flask fitted with a mechanical stirrer, reflux condenser, and dropping funnel was placed 1 l. of ether. The ether was cooled in an ice water bath and 50 g (0.37 mol) of aluminum chloride was added cautiously. The mixture was stirred at ice temperature for 10 min and 50 g (1.31 mol) of lithium aluminum hydride was carefully added. The mixture was allowed to warm to room temperature and 330 g (1.84 mol) of *exo*-2,3-epoxy-*trans*-5,6-dichlorobicyclo[2.2.1]heptane in 1.8 l. of ether was added over a period of 1 hr. The mixture was heated at reflux for 72 hr and then was cooled in an ice water bath. After the cautious addition of 200 ml of water, the mixture was allowed to stir for 1.5 hr at room temperature. The solids were filtered and washed twice with 300 ml of ether. After drying over magnesium sulfate, the ether was removed by distillation. Traces of remaining ether were removed using a rotary evaporator, leaving 314 g (94%) of a clear liquid which solidified on standing. An analytical sample was prepared by two recrystallizations from hexane and sublimation at 50° (0.5 mm), mp 58–60°.

*Anal.* Calcd for $C_7H_{10}Cl_2O$: C, 46.4; H, 5.6; Cl, 39.2. Found: C, 46.5, 46.3; H, 5.6, 5.5; Cl, 39.0, 39.2.

The nmr spectrum showed absorption at $\tau$ 5.75 (2 H, m), 6.42 (1 H, m), 7.42 (1 H, s), 7.60 (2 H, m), and 7.90–8.70 (4 H, m).

*trans*-5,6-Dichloro-2-norcamphor.—To a solution of 300 g (1.66 mol) of *trans*-5,6-dichloro-*exo*-2-hydroxybicyclo[2.2.1]heptane in 2 l. of ether was added a solution of 333 g (2.0 equiv) of sodium dichromate and 250 ml of concentrated sulfuric acid in 1.6 l. of water. The cooled chromic acid solution was added at a rate to maintain moderate reflux (2 hr). The mixture was stirred for an additional 5 hr at room temperature. The aqueous layer was separated and extracted with four 250-ml portions of ether. The combined ether solutions were washed three times with 250 ml of 5% sodium carbonate solution, twice with 250 ml of water, and twice with 250 ml of saturated sodium chloride solution. After drying over magnesium sulfate, the ether was removed by distillation. The residual ether was removed using a rotary evaporator, leaving 279 g (93%) of a colorless liquid which solidified on standing. An analytical sample was prepared by two recrystallizations from hexane and sublimation at 60° (0.5 mm), mp 77.0–77.4°.

*Anal.* Calcd for $C_7H_8Cl_2O$: C, 47.0; H, 4.5; Cl, 39.6. Found: C, 46.9, 47.0; H, 4.3, 4.3; Cl, 39.5, 39.5.

The nmr spectrum showed absorption at $\tau$ 5.67 (1 H, pentet, $J$ = 2 Hz), 5.98 (1 H, t, $J$ = 2 Hz), 7.21 (2 H, m), and 7.40–8.32 (4 H, m). The ir spectrum showed absorption at 1772 $cm^{-1}$.

Reaction of *trans*-5,6-Dichloro-2-norcamphor with Potassium *tert*-Butoxide.—A slurry of potassium *tert*-butoxide formed from 5.5 g of potassium in 200 ml of toluene was treated with a solution of 17.9 g (0.1 mol) of *trans*-5,6-dichloro-2-norcamphor in 20 ml of toluene. The mixture was allowed to stir at room temperature for 20 hr. The mixture was shaken with 200 ml of ice water in a separatory funnel. An aqueous layer was drawn off and the toluene was washed with 100 ml of saturated sodium chloride solution. The solution was dried over sodium sulfate and the toluene was removed using a rotary evaporator, giving 13.3 g (93%) of a yellow oil. Analysis by vpc indicated that only one product was formed. The ir spectrum (1770 $cm^{-1}$) and nmr spectra are consistent with the product being *endo*-5-chlorotricyclo-[2.2.1.$0^{2,6}$]heptan-3-one. The nmr spectrum ($CCl_4$) showed absorption at $\tau$ 5.58 (1 H, t, $J$ = 1 Hz), 7.58 (2 H, pentet, $J$ = 6 Hz, split further into multiplets), 8.00 (3 H, m), and 8.50 (1 H, t, $J$ = 6 Hz).

*Anal.* Calcd for $C_7H_7ClO$: C, 59.0; H, 5.0; Cl, 24.9. Found: C, 58.8, 58.9; H, 5.1, 5.1; Cl, 24.8, 24.9.

*trans*-5,6-Dichloronorcamphorquinone.—Into a flask fitted with a mechanical stirrer and water separator were placed 626 g

(5.6 mol) of freshly sublimed selenium dioxide, 915 g (5.1 mol) of *trans*-5,6-dichloro-2-norcamphor, and 1.8 l. of xylene. The flask was heated in an oil bath at 165° for 8 hr, during which time 92 ml (100%) of water was collected. The mixture was stored in a refrigerator overnight and filtered. The solvent was removed under reduced pressure and the residue was divided into three equal portions. Each portion was bulb to bulb distilled at 1–2 mm using an oil bath at 150°, giving a total of 708 g (72%) of an orange, waxy solid, bp 110–130°. The crude diketone was converted immediately to the monotosylhydrazone.

The nmr spectrum ($CCl_4$) showed absorption at $\tau$ 5.40 (1 H, sextet, $J$ = 2 Hz), 5.80 (1 H, t, $J$ = 2 Hz), 6.57 (1 H, m), 6.75 (1 H, pentent, $J$ = 1 Hz), 7.17 (1 H, d, $J$ = 12 Hz, split further into triplets, $J$ = 1 Hz), 7.74 (1 H, d, $J$ = 12 Hz, split further into quartets, $J$ = 1 Hz). The ir spectrum showed absorption at 1756 and 1790 $cm^{-1}$.

***trans*-5,6-Dichlorodiazonorcamphor.**—To a solution of 225 g (1.32 mol) of *trans*-5,6-dichloronorcamphorquinone and 350 ml of glacial acetic acid cooled in an ice water bath was added a boiling solution of 234 g (1.26 mol) of *p*-toluenesulfonylhydrazide in 300 ml of acetic acid at a rate to maintain the temperature below 15°. The stirring was continued until precipitation occurred. The mixture was stored in a refrigerator overnight and filtered. The solid was mixed with 1.5 l. of water and again filtered. After it was dried in the atmosphere for 24 hr and then under reduced pressure over phosphorus pentoxide, there was obtained 267 g (56%) of the cream colored monotosylhydrazone, mp 160–161° dec.

The tosylhydrazone (30.0 g, 83.2 mmol) was ground to a fine powder and mixed with 100 g of 80–200 mesh basic alumina in a 250-ml flask. Chloroform (70 ml) was added and the wetted mixture was stirred with a spatula until it was of a uniform consistency. The mixture was poured onto a column (65 mm diameter) containing 130 g of alumina and was eluted with chloroform until the eluent was colorless. The eluents from five runs were combined and the chloroform was distilled until the volume was 300 ml. The remaining solvent was removed using a rotary evaporator, giving 75.2 g (88%) of an orange oil which solidified on standing. The diazo ketone could be purified by recrystallization from *n*-hexane–cyclohexane and was obtained as needles, mp 88.4–89.2°.

*Anal.* Calcd for $C_7H_6Cl_2N_2O$: C, 41.0; H, 3.0; Cl, 34.6; N, 13.7. Found: C, 40.9, 41.0; H, 2.9, 3.0; Cl, 34.6, 34.6; N, 13.7, 13.8.

The nmr spectrum ($CDCl_3$) showed absorption at $\tau$ 5.62 (2 H, m), 6.40 (1 H, m), 7.04 (1 H, m), and 7.74 (2 H, m). The ir spectrum showed absorption at 1710 (C=O) and 2090 $cm^{-1}$ (C=$N_2$).

**Methyl *trans*-2,3-Dichlorobicyclo[2.1.1]hexane-5-carboxylate.**—A solution of 66.7 g (0.33 mol) of *trans*-5,6-dichlorodiazonorcamphor in 2.5 l. of absolute methanol was irradiated with a water-cooled Hanovia 450-W quartz immersion lamp using a Corex filter. After 72 hr, 6.6 l. (90%) of nitrogen was evolved. The solution was concentrated to 100 ml using a rotary evaporator. The residue was diluted with 250 ml of ether and the ether solution was washed with 100 ml of cold water, 100 ml of saturated sodium carbonate solution, and twice with 100 ml of saturated sodium chloride solution. The ether solution was dried over magnesium sulfate and the solvent was removed using a rotary evaporator. Distillation of the residue gave 44.4 g (66%) of methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-carboxylate, bp 86–88° (0.5 mm). Vpc analysis on a 10 ft × 0.375 in. 20% DEGS column at 160° showed that the product consisted of 85% of the endo epimer (18 min) and 15% of the exo epimer (13 min). Analytical samples were obtained by collection of the corresponding peaks.

*Anal.* Calcd for $C_8H_{10}Cl_2O_2$: C, 46.0; Cl, 33.9. Found: endo, C, 46.0, 45.7; H, 5.0, 5.0; Cl, 33.7, 33.8; exo, C, 46.1, 46.0; H, 4.9, 4.8; Cl, 33.9, 33.8.

***endo*- and *exo*-*trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-carboxylic Acids.**—A solution of 10.0 g (48 mmol) of methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-carboxylate in 30 ml of methanol was added to a solution of 5.3 g (94 mmol) of potassium hydroxide in 65 ml of methanol at room temperature. The mixture was stirred at reflux for 2 hr and then poured into 500 ml of ice water. The aqueous layer was washed three times with 150 ml of ether and then acidified with hydrochloric acid. The solution was extracted three times with 150 ml of ether. After the solution was dried over magnesium sulfate and solvent was removed with a rotary evaporator, there was obtained 7.0 g (75%) of a yellow oil which partially solidified on standing. An nmr analysis indicated a 1:1 mixture of exo and endo acids. The crude acids were dissolved in 50 ml of hot carbon tetrachloride and the solution was decolorized with charcoal. On cooling, 1.8 g of the endo acid precipitated, mp 83–85°. Removal of the solvent from the filtrate followed by recrystallization from hexane gave 4.8 g of a 3:1 mixture of the exo and endo acids. The pure endo acid could be obtained by further recrystallization from hexane, mp 151–152.6°.

The ether extract of the basic solution was evaporated, giving 1.5 g of a 1:1 mixture of endo and exo carboxylic esters.

*Andl.* Calcd for $C_7H_8Cl_2O_2$: C, 43.1; H, 4.1; Cl, 36.4. Found: endo, C, 43.1, 43.0; H, 4.2, 4.2; Cl, 36.2, 36.3; exo, C, 43.3, 43.3; H, 4.2, 4.3; Cl, 36.3, 36.3.

The acids could also be obtained directly *via* the photolysis of the diazo ketone in aqueous dioxane. Using a solution of 49.0 g of the diazo ketone in 1600 ml of aqueous dioxane (75 ml of dioxane to 200 ml of water) and irradiating for 48 hr, 88% of the theoretical amount of nitrogen was evolved. The acid mixture was isolated as described above, giving 26.7 g (57%) of an 85:15 mixture of the endo and exo acids.

**Methyl Bicyclo[2.1.1]hexene-*endo*-5-carboxylate.**—A mixture of 1.5 g (62 g-atoms) of 20 mesh granular magnesium and 150 g of mercury was placed in a 3 × 0.5 in. iron pipe which was then capped at both ends. The pipe was heated with a Bunsen burner for 3 hr and allowed to cool. The content was scraped into a 250-ml three-necked flask with a helium inlet, Herschberg stirrer, and reflux condenser with a drying tube. The amalgam was covered with 40 ml of glyme, and a solution of 3.0 g (14 mmol) of pure methyl *trans*-2,3-dichlorobicyclo[2.1.1]-*endo*-5-carboxylate in 40 ml of glyme was added with stirring. The mixture was heated at reflux for 9 days. The supernatant suspension was decanted into a 250-ml centrifuge bottle and the solids remaining in the flask were washed three times with 50 ml of ether and twice with 50 ml of pentane. The combined organic solution was centrifuged and then washed five times with 100 ml of water and twice with 100 ml of saturated salt solution. After the solution was dried over magnesium sulfate, the solvent was distilled through a 12-ft Vigreux column until a residue of 5 ml remained. This was separated by preparative vpc (10 ft × 0.375 in. 20% DEGS at 155°) into two components with retention times of 2.5 and 25 min. The more volatile component (60% of the mixture) was methyl bicyclo[2.1.1]hexene-*endo*-5-carboxylate. The minor component was unreacted starting material.

*Anal.* Calcd for $C_8H_{10}O_2$: C, 69.5; H, 7.3. Found: C, 69.3, 69.4; H, 7.2, 7.4.

The ir spectrum had a carbonyl band at 1738 $cm^{-1}$.

The ester could also be prepared using the phenanthrene dianion. A mixture of 1.78 g (10 mmol) of phenanthrene, 0.46 g (20 g-atoms) of sodium, and 50 ml of glyme was stirred under a nitrogen atmosphere. After 0.5 hr, the mixture turned dark green. Stirring was continued for 2 hr at room temperature. The green solution was cooled to −40° in a Dry Ice–methanol bath and 1.0 g (4.8 mmol) of methyl *trans*-2,3-dichlorobicyclo[2.1.1]-hexane-*endo*-5-carboxylate in 10 ml of glyme was added over a period of 10 min. After stirring for 2 hr at −40°, the solution was poured into 100 ml of ether and 100 ml of ice water. The layers were separated and the aqueous layer was washed with 80 ml of ether. The combined ether solutions were washed with 60 ml of water and 60 ml of saturated salt solution, and dried over sodium sulfate. The ether was distilled through an 18-in. packed column and the residue (0.9 g) was separated by preparative vpc into three components with retention times of 7, 20, and 34 min. They were identified as methyl bicyclo[2.1.1]hexene-*endo*-5-carboxylate (35%), and *exo*- (35%) and *endo*- (30%) methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-carboxylates.

**Hydrogenation of Methyl Bicyclo[2.1.1]hexene-*endo*-5-carboxylate.**—A mixture of 60 mg of the ester, 5 mg of 5% palladium on carbon catalyst, and 1 ml of dry methanol was treated with hydrogen for 2.5 hr at room temperature. The product was analyzed by vpc (10 ft × 0.375 in. 20% DEGS at 135°) and found to be a single component. The product was collected and shown to be methyl bicyclo[2.1.1]hexane-*endo*-5-carboxylate by comparison of ir and nmr spectra with those of an authentic sample.[14]

***trans*-2,3-Dichlorobicyclo[2.1.1]hexane-*endo*-5-methanol.**—A solution of 10.0 g (48 mmol) of methyl *trans*-2,3-dichlorobicyclo-[2.1.1]hexane-*endo*-5-carboxylate in 30 ml of ether was added to 5.0 g (130 mmol) of lithium aluminum hydride in 30 ml of ether. After stirring for 4 hr, the mixture was worked up in the usual

fashion, giving 7.6 g (87%) of *trans*-2,3-dichlorobicyclo[2.1.1]-hexane-*endo*-5-methanol, bp 79–80° (0.1 mm).

*Anal.* Calcd for $C_7H_{10}Cl_2O$: C, 46.4; H, 5.6; Cl, 39.2. Found: C, 46.4, 46.4; H, 5.7, 5.6; Cl, 39.0, 39.0.

**Bicyclo[2.1.1]hexene-*endo*-5-methanol.**—Magnesium amalgam prepared from 3.0 g of magnesium and 300 g of mercury was covered with 50 ml of glyme. A solution of 5.0 g (28 mmol) of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-methanol in 10 ml of glyme was added and the mixture was vigorously stirred at reflux for 48 hr. Ether (400 ml) was added and the mixture was cooled in an ice water bath. Water (200 ml) was cautiously added and the cold mixture was stirred for 1 hr. The solids were separated by centrifugation and washed with 600 ml of ether. The combined ether solution was washed with 100 ml of saturated salt solution, dried over potassium carbonate, and concentrated to 35 ml by distillation through a 12-in. Vigreux column. The solution was transferred to a small flask and the glyme was removed by distillation at 20° (0.1 mm). The product was collected by raising the bath temperature to 60°, giving 1.05 g of distillate. It was analyzed by preparative vpc (10 ft × 0.375 in. 5% Carbowax 20M at 100°), and 412 mg (14%) of bicyclo[2.1.1]hexene-*endo*-5-methanol was collected.

*Anal.* Calcd for $C_7H_{10}O$: C, 76.3; H, 9.2. Found: C, 76.2, 76.2; H, 9.1, 9.1.

The dehalogenation was also effected using sodium phenanthrene formed from 3.56 g (20 mmol) of phenanthrene, 1.5 g (65 mg-atoms) of sodium, and 60 ml of glyme. To a solution of 1.0 g (5.5 mmol) of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-methanol was added at −40° the sodium phenanthrene solution until the dark green color persisted. The mixture was poured into 300 ml of ice water and extracted twice with 150 ml of ether. The ether solution was washed with 100 ml of saturated salt solution, dried over sodium sulfate, and distilled through an 18-in. packed column to remove the solvent. Most of the glyme was removed by distillation (20 mm, 40°) and the residue was distilled at 0.5 mm (bath temperature 85°), giving 2 g of distillate. The latter was found by vpc to contain 0.5 g (80%) of bicyclo[2.1.1]hexene-*endo*-5-carboxylate along with glyme.

***trans*-2,3-Dichlorobicyclo[2.1.1]hexane-*exo*-5-methanol.**—2,3-Dichlorobicyclo[2.1.1]hexane-*exo*-5-carboxylic acid (25% endo) was converted to its methyl ester with diazomethane. A solution of 22.8 g (0.11 mol) of the ester in 50 ml of ether was added to 5.0 g (0.13 mol) of lithium aluminum hydride in 250 ml of ether. After the usual work-up there was obtained 17.0 g (86%) of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-5-methanol, bp 58–72° (0.1 mm). Nmr analysis indicated it to be 77% exo and 23% endo.

Vpc collection (10 ft × 0.375 in., 5% Carbowax 20M at 175°) gave a pure sample of the exo isomer (exo, 22 min; endo, 31 min).

*Anal.* Calcd for $C_7H_{10}Cl_2O$: C, 46.4; H, 5.6; Cl, 39.2. Found: C, 46.2, 46.1; H, 5.9, 6.0; Cl, 38.9, 38.8.

**Bicyclo[2.1.1]hexene-*exo*-5-methanol.**—The dehalogenation of 4.0 g of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*exo*-5-methanol (23% endo) with magnesium amalgam was carried out as described above. There was obtained 522 mg (22%) of bicyclo-[2.1.1]hexene-*exo*-5-methanol and 150 mg (6%) of bicyclo[2.2.1]-hexene-*endo*-5-methanol.

*Anal.* Calcd for $C_7H_{10}O$: C, 76.3; H, 9.2. Found: C, 76.1, 76.2; H, 9.1, 9.0.

**Methyl *trans*-2,3-Dichlorobicyclo[2.1.1]hexane-*endo*-5-acetate.**—A mixture of 26.3 g of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-earboxylic acid and 50 g of thionyl chloride was heated at reflux for 3 hr and distilled, giving 23.2 g (84%) of *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-carbonyl chloride, bp 91–92° (1.1 mm).

An ether solution of diazomethane was prepared by adding 28.0 g of *N*-methyl-*N*-nitrosourea to an ice-cooled mixture of 100 ml of 40% potassium hydroxide solution and 400 ml of ether. The ether layer was dried at 0° for 8 hr over potassium hydroxide pellets. The ether solution was transferred to a clean flask and triethylamine (9.5 g) was added. After the solution was cooled in an ice–salt bath, 20.0 g of the acid chloride in 100 ml of ether was added over 0.5 hr with vigorous stirring. The mixture was filtered and concentrated using a rotary evaporator, giving 21.3 g of a dark orange oil.

A solution of the diazo ketone in 60 ml of methanol was added to a boiling suspension of 0.5 g of silver oxide in 100 ml of methanol. The mixture was vigorously stirred at reflux for 5 hr with 0.5-g portions of silver oxide added hourly. The mixture was cooled in a ice bath and filtered. The solid was washed twice with 50 ml of ether. The orange solution was concentrated to 30 ml using a rotary evaporator. The residue was diluted with 200 ml of ether, and the solution was washed with 100 ml of water and 100 ml of saturated salt solution. After drying over magnesium sulfate, the solvent was removed using a rotary evaporator. The residue was distilled, giving 17.7 g (82%) of methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-acetate, bp 77–78° (0.15 mm).

*Anal.* Calcd for $C_9H_{12}Cl_2O_2$: C, 48.5; H, 5.4; Cl, 31.8. Found: C, 48.4, 48.2; H, 5.3, 5.4; Cl, 31.7, 31.7.

**2-(*trans*-2,3-Dichlorobicyclo[2.1.1]hex-*endo*-5-yl)ethanol.**—A solution of 17.0 g (76 mmol) of methyl *trans*-2,3-dichlorobicyclo-[2.1.1]hexane-*endo*-5-acetate in 40 mi of ether was added to 4.0 g (105 mmol) of lithium aluminum hydride in 100 ml of ether with stirring. After 2 hr the mixture was worked up in the usual fashion, giving 14.0 g (94%) of 2-(*trans*-2,3-dichlorobicyclo-[2.1.1]hex-*endo*-5-yl)ethanol, bp 99–100° (0.4 mm). Vpc analysis indicated the materials to be homogeneous.

*Anal.* Calcd for $C_8H_{12}Cl_2O$: C, 49.3; H, 6.2; Cl, 36.4. Found: C, 49.1, 49.1; H, 6.3, 6.2; Cl, 36.3, 36.3.

**2-(Bicyclo[2.1.1]hexen-*endo*-5-yl)ethanol.**—A mixture of 4.0 g (21 mmol) of *trans*-2,3-dichlorobicyclo[2 1.1]hexane-*endo*-5-ethanol, magnesium amalgam (1.5 g of magnesium and 150 g of mercury), and 50 ml of glyme was vigorously stirred at reflux for 24 hr. The mixture was worked up as described above, giving 970 mg (38%) of 2-(bicyclo[2.1.1]hexen-*endo*-5-yl)ethanol (10 ft × 0.375 in., 5% Carbowax 20M column at 155°).

*Anal.* Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.3, 77.2; H, 10.2, 10.3.

The alcohol also was prepared using sodium phenanthrene prepared from 6.0 g (34 mmol) of phenanthrene and 2.5 g (110 mmol) of sodium in 80 ml of dimethyl ether at −40°. The solution was cooled to −60° and 6.0 g (31 mmol) of 2-(*trans*-2,3-dichlorobicyclo[2.1.1]hex-*endo*-5-yl)ethanol was slowly added with stirring. After an additional hour at −40°, 40 ml of diethyl ether and 2 ml of water were added. The mixture was allowed to warm to 0° to distil the dimethyl ether. It was poured into 300 ml of ice water and extracted twice with 150 ml of ether. The ether solution was cooled with saturated salt solution, dried over magnesium sulfate, and distilled, giving 3.8 g (99%) of 2-(bicyclo[2.1.1]hexen-*endo*-5-yl)ethanol, bp 50–55° (2 mm).

**2-(*anti*-Tricyclo[3.1.1.0$^{2,4}$]hept-*endo*-6-yl)ethanol.**—2-(Bicyclo-[2.1.1]hexen-*endo*-5-yl)ethanol (3.8 g) was converted to the acetate (4.8 g, 95%) with pyridine and acetic anhydride. The acetate (3.0 g) was placed in a flask along with 7 ml of *n*-hexane and 200 mg of freshly prepared cuprous bromide. The mixture was treated with diazomethane prepared from 20 g of *N*-methyl-*N*-nitrosourea, 200 ml of 33% potassium hydroxide solution, and 50 ml of decalin as described previously.[23] The reaction was followed by vpc using a 10 ft × 0.375 in. 5% Carbowax 20M column at 135°. The reaction mixture was filtered and the solid was washed with dry ether. The ether solution was added to 2.0 g of lithium aluminum hydride in 50 ml of ether, and after stirring for 1 hr, the mixture was worked up in the usual fashion, giving 2.1 g (85%) of 2-(*anti*-tricyclo[3.1.1.0$^{2,4}$]hept-*endo*-6-yl)ethanol, bp 58–60° (2 mm).

*Anal.* Calcd for $C_9H_{14}O$: C, 78.2; H, 10.2. Found: C, 77.6, 77.6; H, 10.1, 10.2.

**Methyl *trans*-2,3-Dichlorobicyclo[2.1.1]hexyl-*endo*-5 Ketone.**—To a solution of 30 g (0.32 mol) of dimethylzinc in 600 ml of pentane was added 20.0 g (93 mmol) of *trans*-2,3-dichlorobicyclo-[2.1.1]hexane-*endo*-5-carbonyl chloride in 150 ml of pentane. The solution was stirred to reflux for 6 hr, during which time an orange oil separated. The mixture was cooled in an ice water bath and 300 ml of saturated ammonium chloride solution was cautiously added. The pentane layer was washed with 100 ml of water, 100 ml of saturated sodium carbonate solution, and 100 ml of saturated salt solution. It was dried over sodium sulfate, the pentane was removed using a rotary evaporator, and the residue was distilled, giving 18.0 g (98%) of the ketone, bp 73–76° (0.2 mm).

*Anal.* Calcd for $C_8H_{10}Cl_2O$: C, 49.8; H, 5.2; Cl, 36.7. Found: C, 49.7, 49.9; H, 5.4. 5.4; Cl, 36.6, 36.7.

***trans*-2,3-Dichlorobicyclo[2.1.1]hexyl *endo*-5-Acetate.**—A solution of trifluoroperacetic acid in methylene chloride was prepared from 2.8 ml of 90% hydrogen peroxide, 100 ml of methylene chloride, and 20.0 g of trifluoroacetic anhydride. To the solution was added 0.8 ml of trifluoroacetic acid and 9.1 g (47 mmol) of

(23) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexyl-*endo*-5 ketone in 20 ml of methylene chloride. The solution was stirred for 1 hr at 0° and 24 hr at room temperature. It was poured into 100 g of ice water, the mixture was shaken vigorously, and the methylene chloride layer was separated. After the mixture was washed with 100 ml of 5% sodium carbonate solution and 100 ml of saturated salt solution and dried over magnesium sulfate, distillation gave 8.2 g (83%) of *trans*-2,3-dichlorobicyclo[2.1.1]hexyl *endo*-5-acetate, bp 60–65° (0.1 mm). Vpc analysis indicated 80% purity, with 10% of methyl *trans*-2,3-dichlorobicyclo[2.1.1]-hexane-*endo*-5-carboxylate and 10% of unidentified impurities. An analytical sample was collected by vpc.

*Anal.* Calcd for $C_8H_{10}Cl_2O_2$: C, 46.0; H, 4.8; Cl, 33.9. Found: C, 45.8, 45.7; H, 4.8, 4.8; Cl, 34.0, 34.0.

**Attempted Dehalogenation of *trans*-2,3-Dichlorobicyclo[2.1.1]-hexyl *endo*-5-Acetate.**—The dehalogenation with magnesium amalgam as described above was carried out for 7 days. The only products formed were methyl bicyclo[2.1.1]hexene-*endo*-5-carboxylate (formed from the 10% dichloro ester impurity) and benzene. The dehalogenation with sodium phenanthrene also was carried out as described above. The product was separated by vpc (10 ft × 0.375 in. 5% Carbowax 20M at 115°) into four components with retention times of 2, 6, 7.5, and 10 min. The first component appeared to be 1,2-di($\Delta^3$-cyclopentenyl)ethane (10%). The second and third components were identified as *exo*-bicyclo[3.1.0]hex-3-en-2-ol (70%) (identified by hydrogenation to the known *exo*-bicyclo[3.1.0]hexanol-2)[24] and $\Delta^3$-cyclopentenylmethanol (10%). The fourth component (10%) appeared to be a mixture and was not identified.

***trans*-2,3-Dichlorobicyclo[2.1.1]hexan-*endo*-5-ol.**—An ether solution of methyllithium was prepared from 2.0 g of lithium, 150 ml of anhydrous ether, and methyl bromide. A solution of 5.0 g (24 mmol) of *trans*-2,3-dichlorobicyclo[2.1.1]hexyl *endo*-5-acetate (80% pure) in 75 ml of ether was cooled in an ice–salt bath and 72 ml (1.5 equiv) of the methyllithium solution was added over a period of 10 min with stirring. After stirring for an additional 5 min, the solution was added dropwise to a rapidly stirred mixture of 100 ml of saturated ammonium chloride solution and 100 ml of chipped ice. The ether layer was washed twice with 100 ml of water, and twice with saturated salt solution. After the solution was dried over magnesium sulfate, the solvent was removed using a rotary evaporator, giving 4.5 g of a semisolid. The residue was dissolved in 10 ml of carbon tetrachloride. Cooling afforded 1.5 g (37%) of long white needles. The filtrate contained an additional 30% of the alcohol. After recrystallization from hexane–cyclohexane it had mp 88.8–90.6°.

*Anal.* Calcd for $C_6H_8Cl_2O$: C, 43.1; H, 4.8; Cl, 42.5. Found: C, 43.0, 43.1; H, 5.2, 5.2; Cl, 42.4, 42.5.

(24) E. J. Corey and R. L. Dawson, *J. Amer. Chem. Soc.*, **85**, 1782 (1963).

**Reduction of *trans*-2,3-Dichlorobicyclo[2.1.1]hexyl *endo*-5-Acetate with Lithium Aluminum Hydride.**—A solution of 0.5 g of *trans*-2,3-dichlorobicyclo[2.1.1]hexyl *endo*-5-acetate (80% pure) in 10 ml of ether was added to 200 mg of lithium aluminum hydride in 30 ml of ether. After the usual work-up, the residue (0.2 g, 50%) was analyzed by vpc (10 ft × 0.375 in. 5% Carbowax 20M at 165°) and found to contain four components with retention times of 14, 16, 30, and 35 min. The first component (45%) was *trans*-2,3-dichlorobicyclo[2.1.1]hexan-*endo*-5-ol. The second (17%) was *trans*-3-chloro-*cis*-2-chloro-*trans*-4-hydroxybicyclo[3.1.0]hexane, and the third (15%) was *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-methanol (from the methyl ester impurity). The fourth component (20%) was not identified.

**Hydrolysis of *trans*-2,3-Dichlorobicyclo[2.1.1]hexyl *endo*-5-Acetate.**—A mixture of 1.0 g of the acetate, 10 ml of 1 *N* sodium hydroxide solution, and 20 ml of ether was stirred at room temperature for 8 hr. The ether layer was washed with saturated salt solution and dried over magnesium sulfate. Removal of the solvent using a rotary evaporator gave 0.5 g of a yellow oil. It was separated into five components with retention times of 5, 10, 13, 16, and 34 min by vpc. The ratios were 2:5:2:2:1. The major component was unchanged starting material. The first component appeared to be 2-chloro-*trans*-4-hydroxybicyclo-[3.1.0]hex-2-ene. The third component was a 1:1 mixture of two compounds, one of which was methyl *trans*-2,3-dichlorobicyclo[2.1.1]hexane-*endo*-5-carboxylate (present in the reactant). The fourth was *cis*-2-chloro-*trans*-3-chloro-*trans*-4-hydroxybicyclo[3.1.0]hexane. The fifth was identical with the last component from the lithium aluminum hydride reduction.

**Attempted Dehalogenation of *trans*-2,3-Dichlorobicyclo[2.1.1]-hexan-*endo*-5-ol.**—The reaction of 1.0 g of the alcohol with magnesium amalgam formed from 1.5 g of magnesium and 150 g of mercury was carried out as described above. Vpc analysis of the product (10 ft × 0.375 in. 5% Carbowax 20M at 120°) showed four components with retention times of 5, 6, 7.5, and 8.5 min. The major component (8.5 min, 85%) was identified as $\Delta^3$-cyclopentenylmethanol, and the third component was found to be $\Delta^2$-cyclopentenylmethanol. The remaining components were not identified because of their low concentration.

The reaction of 0.5 g of the alcohol with sodium phenanthrene in dimethyl ether was carried out using the procedure described above. The residue was analyzed by nmr and none of the desired olefinic alcohol was found. Vpc analysis was not successful because of the apparent thermal instability of the product.

**Registry No.**—*exo*-**7**, 35672-74-3; **8**, 35672-75-4; **9**, 823-71-2; **10**, 35672-77-6; **10** monotosylhydrazone, 35655-59-5; **11**, 35672-78-7; **20**, 35672-79-8.

# The Structures and Syntheses of Two Dihydropyrindines Isolated from California Petroleum[1]

S. A. MONTI,* ROBERT R. SCHMIDT, III, B. A. SHOULDERS, AND H. L. LOCHTE

*Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712*

*Received June 8, 1972*

The structures of two nitrogen bases isolated from California petroleum have been assigned as *trans*-5,7-dimethyl-6,7-dihydro-5*H*-1-pyrindine and 5,7,7-trimethyl-6,7-dihydro-5*H*-1-pyrindine on the basis of spectral and synthetic studies. The *cis*-5,7-dimethyl and the 5,5,7-trimethyl analogs were prepared also. An improved synthesis of the 1-pyrindone nucleus is described. The nmr spectra of various 6,7-dihydro-5*H*-1-pyrindines are presented.

The occurrence of nitrogen bases as minor constituents of petroleum has led to numerous studies on the nature of these substances.[2] In general these bases are simple alkyl derivatives of pyridine, quinoline, and related benzo analogs, although a few more complex compounds have been identified.[2,3]

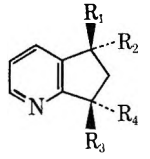
We wish to report the structure elucidations and syntheses of two new bases isolated from California

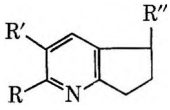
(1) Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

(2) (a) H. L. Lochte and E. R. Littman, "The Petroleum Acids and Bases," Chemical Publishing Co., New York, N. Y., 1955; (b) L. R. Snyder, *Accounts Chem. Res.*, **3**, 290 (1970).

(3) (a) L. R. Snyder, *Anal. Chem.*, **41**, 1084 (1960); (b) L. R. Snyder and B. E. Buell, *ibid.*, **40**, 1295 (1968); (c) E. J. Buell, *ibid.*, **39**, 756 (1967); (d) D. K. Albert, *ibid.*, **39**, 1113 (1967); (e) H. V. Drushel and A. J. Sommers, *ibid.*, **38**, 19 (1966); D. R. Latham and W. E. Haines, *ibid.*, **37**, 54 (1965).

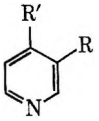
petroleum: *trans*-5,7-dimethyl-6,7-dihydro-5*H*-1-pyrindine (**1**) and 5,7,7-trimethyl-6,7-dihydro-5*H*-1-pyrindine (**2**). The parent base **5**[4a] and the three monomethyl analogs **6a**–**c**[4b–e] have been isolated previously from petroleum sources.





**1**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
**2**, $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$
**3**, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
**4**, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$

**5**, $R = R' = R'' = H$
**6a**, $R = CH_3$; $R' = R'' = H$
**b**, $R' = CH_3$; $R = R'' = H$
**c**, $R'' = CH_3$; $R = R' = H$



**7**, R = cyclopentyl; R′ = H
**8**, R = H; R′ = cyclopentyl

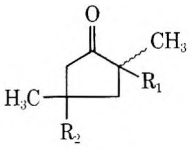
## Results and Discussion

A preliminary structural assignment[5] of the two bases under consideration, originally characterized as picrates A and B, as the isomeric 3- and 4-cyclopentylpyridines (**7**, **8**) ($C_{10}H_{13}N$) was retracted upon synthesis of authentic **7** and **8**.[6] Reexamination of these substances by high-resolution mass spectroscopy[7] revealed that the base derived from picrate A has the expected composition $C_{10}H_{13}N$, while the base from picrate B corresponds to the empirical formula $C_{11}H_{15}N$. The nmr spectra for picrates A and B indicated that both materials were *ca.* 80–90% pure; the chemical shift data for the predominant isomer in each case are given in the Experimental Section.

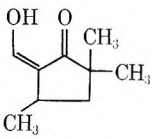
Consideration of the nmr data suggests that both bases possess a 6,7-dihydro-5*H*-1-pyrindine (**5**) nucleus. The presence of two doublet methyl groups and a methylene group (δ 2.20 ppm) remote from the pyridine nucleus[8] in the base corresponding to picrate A is consistent with the tentative assignment of this material as either *cis*- or *trans*-5,7-dimethyl-6,7-dihydro-5*H*-1-pyrindine (**3** or **1**). In an analogous fashion, the base derived from B is in accord with either the 5,5,7-trimethyl- or 5,7,7-trimethyldihydropyrindine structure (**4** or **2**). In order to confirm these tentative skeleton assignments and to resolve the geometric isomer uncertainty in the dimethyl base and the position isomer ambiguity in the trimethyl base, the synthesis of these four substances was undertaken.

The trimethyl-2-pyridones **13** and **14** were prepared from the trimethylcyclopentanones **10**[10] and **11**[11] *via* Michael addition of cyanoacetamide[12] to the corresponding hydroxymethylene derivatives (*e.g.*, **12**). The resulting adducts (part structure **15**) furnished **13** and **14** upon treatment with hydrochloric acid.

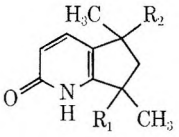
From a synthetic point of view the key cyanoacetamide addition step proceeded in only a modest yield (*ca.* 25%). Accordingly the behavior of the *n*-butylthiomethylene derivative (**16**) of 2,4-dimethylcyclopentanone (**9**)[13] was examined in this Michael reaction. Although no reaction was observed when **16** was treated with cyanoacetamide under the normal conditions,[12] *e.g.*, piperidine–ethanol at 40°, smooth conversion did occur when the substrates were heated at reflux with sodium ethoxide in ethanol. Spectral data indicated that the resulting adduct, obtained in 68% yield, was the 3-cyano-2-pyridone **17**. Hydrochloric acid treatment of **17** yielded a cis–trans mixture of the dimethyl-2-pyridone **18**.



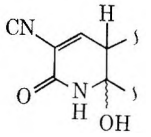
**9**, $R_1 = R_2 = H$
**10**, $R_1 = H$; $R_2 = CH_3$
**11**, $R_1 = CH_3$; $R_2 = H$



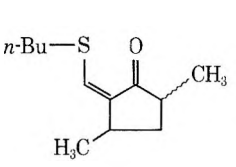
**12**



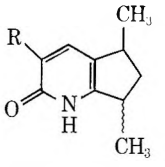
**13**, $R_1 = H$; $R_2 = CH_3$
**14**, $R_1 = CH_3$; $R_2 = H$



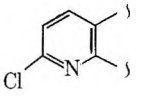
**15**



**16**



**17**, R = CN
**18**, R = H



**19**

Conversion of the 2-pyridones **13**, **14**, and **18** to the corresponding dihydro-5*H*-1-pyrindines **4**, **2**, and **1** and **3**, respectively, was unexceptional; treatment with dichlorophenylphosphene oxide furnished the 2-chloro-derivatives **19**, then either chemical or catalytic (preferred) reduction of **19** yielded the desired pyrindines. The nmr data for the free bases and for their picrates are summarized in Table I. In addition, data for some other dihydro-5*H*-1-pyrindine derivatives are included in Table I.

These data unambiguously identify the naturally occurring trimethyl compound, B, as the 5,7,7 isomer **2**. The mixture melting point of picrate B and the

(4) (a) J. Eguchi, *Bull. Chem. Soc. Jap.*, **3**, 235 (1928); (b) P. Arnall, *J. Chem. Soc.*, 1702 (1958); (c) H. L. Lochte and A. G. Pittman, *J. Amer. Chem. Soc.*, **82**, 469 (1960); (d) H. Suzumura, *Bull. Chem. Soc. Jap.*, **34**, 1097 (1959); (e) H. L. Lochte and A. G. Pittman, *J. Org. Chem.*, **25**, 1462 (1960).

(5) H. L. Lochte, E. D. Thomas, and P. Truitt, *J. Amer. Chem. Soc.*, **66**, 550 (1944).

(6) H. L. Lochte and E. N. Wheeler, *ibid.*, **76**, 5548 (1954).

(7) We wish to thank Professor C. Cone for his assistance in obtaining the high-resolution mass spectra data.

(8) Typical chemical shifts for methylene groups bonded to pyridine rings: $C_7$–$CH_2$–, δ 2.78;[9a] $C_3$–$CH_2$–, 2.61;[9b] $C_4$–$CH_2$–, 2.59[9c] ppm.

(9) Sadtler Standard Spectra, NMR Spectra, Sadtler Research Laboratories, Philadelphia, Pa: (a) spectrum no. 7556; (b) spectrum no. 6074; (c) spectrum no. 7557.

(10) (a) R. L. Wasson and H. O. House, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 552; (b) G. D. Ryerson, R. L. Wasson, and H. O. House, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 957.

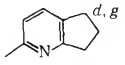
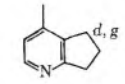
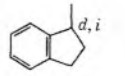
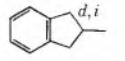
(11) Prepared by a modification of S. F. Birch and E. A. Johnson, *J. Chem. Soc.*, 1493 (1951). The resulting mixture of ketones (**10**, **11**) was separated efficiently by selective formation of the hydroxymethylene derivative **12** of the *less* hindered ketone **11**.

(12) W. C. Thompson, *J. Amer. Chem. Soc.*, **53**, 3160 (1931).

(13) D. Klamann and W. Lache, *Brennst.-Chem.*, **45**, 33 (1964).

TABLE I

NMR DATA FOR SOME 6,7-DIHYDRO-5*H*-1-PYRINDINES[a]

| Compd | C-5 H | C-6 $H_2$ | C-7 H | Methyl groups |
|---|---|---|---|---|
| **2**[b,c] | 2.9–3.4 (m) | 1.47 (dd, 9, 12)<br>2.15 (dd, 7, 12) | | 1.17 (s), 1.27 (d, 7), 1.34 (s) |
| **2**[d] | 3.3–3.9 (m) | 1.83 (dd, 9, 13)<br>2.45 (dd, 8, 13) | | 1.47 (d, 7), 1.49 (s), 1.60 (s) |
| **4**[b] | | 1.46 (dd, 10, 13)<br>2.16 (dd, 7, 13) | 3.0–3.4 (m) | 1.18 (s), 1.32 (s), 1.35 (d, 7) |
| **4**[d] | | 1.84 (dd, 7, 13)<br>2.46 (dd, 8, 13) | 3.6–4.1 (m) | 1.36 (s), 1.48 (s), 1.51 (d, 7) |
| **1**[b,c,e] | 2.9–3.5 (m) | 1.93 (2 H, t, 6) | 2.9–3.5 (m) | *f* |
| **1**[c,d] | 3.1–4.1 (m) | 2.20 (2 H, m) | 3.1–4.1 (m) | 1.42 (d, 7), 1.42 (d, 7) |
| **3**[b,c,e] | 2.9–3.5 (m) | 1.2–1.5 (m)<br>2.3–2.9 (m) | 2.9–3.5 (m) | *f* |
| **3**[d] | 3.1–4.1 (m) | 1.4–1.8 (m)<br>2.6–3.1 (m) | 3.1–4.1 (m) | 1.46 (d, 7), 1.52 (d, 7) |
|  | 3.13 (t, 7)[h] | 2.33 (qn, 7) | 3.31 (t, 7)[h] | 2.78 (s) |
|  | 3.08 (t, 7)[h] | 2.36 (q, 7) | 3.49 (t, 7)[h] | 2.54 (s) |
|  | 3.2–3.8 (m) | 1.7–2.1 (m)<br>2.4–2.8 (m) | 3.2–3.8 (m) | 1.44 (d, 7) |
|  | *j* | *j* | *j* | 1.38 (d, 6.5) |

[a] Chemical shifts are reported in parts per million downfield from internal TMS, 100-MHz spectra, $CDCl_3$ solvent unless specified otherwise; coupling constants (hertz) in parentheses; q = quartet, qn = quintet. [b] Solvent $CCl_4$. [c] 60-MHz spectrum. [d] Spectrum of picrate salt. [e] Data were obtained on the cis–trans mixture. [f] Overlapping methyl group signals, δ 1.17–1.44 ppm. [g] Reference 4c. [h] Based on data available; these assignments could be reversed. [i] Reference 4e. [j] Complex envelope, δ 2.6–3.9 ppm.

picrate of **2** showed no depression, thus confirming this assignment.

Although separation of the cis and trans isomers in the synthetic dimethyl series could be effected at the 2-pyridone (**18**) stage, considerable equilibration occurred during conversion to the 2-chloro derivative **19**. Thus isomer separation was carried out on the dihydropyrindines by fractional recrystallization of the mixture of picrates. The trans structure **1** was assigned to the picrate which showed a two-proton multiplet at δ 2.20 ppm for the C-6 methylene group. Since *both* C-6 methylene protons in the trans isomer **1** have identically disposed adjacent groups, the common chemical shift for these protons is in accord with the proposed structure. In contrast, the picrate of the other isomer revealed two nonequivalent one-proton signals for the C-6 methylene moiety, multiplets at δ 2.85 and *ca.* 1.5 ppm (partially obscured by the methyl group adsorptions). This is in accord with the nonequivalent nature of the two C-6 protons in the cis structure **3**. Analogous nmr data were observed in the 2-pyridone series and the cis- and trans-isomer assignments were made accordingly.

The nmr data for the naturally occurring base A are in complete agreement with those for the trans isomer **1**, thus establishing both the gross carbon skeleton and the stereochemistry of this material.

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer; nmr spectra were measured on a Varian Associates Model A-60 or HA-100 spectrometer. High-resolution mass spectra were obtained using a CEC Model 21-100 mass spectrometer. The microanalytical determinations were done by the Chemalytics, Inc., Tempe, Ariz.

**100-MHz Nmr Data for Picrates A and B.**—Picrate A[5] had mp 117–119°; nmr ($CDCl_3$) δ 8.60 (d, 1, $J$ = 6 Hz, C-2 H), 7.70 (dd, 1, $J$ = 6, 8 Hz, C-3 H), 8.15 (d, 1, $J$ = 8 Hz, C-4 H), 3.1–4.1 (m, 1, C-5 H), 2.20 (m, 2, C-6 $CH_2$), 3.1–4.1 (1, m, C-7 H), and 1.42 ppm (6, d, $J$ = 7 Hz, C-5 and C-7 $CH_3$ groups).

Picrate B[5] had mp 140–146°; nmr ($CDCl_3$) δ 8.56 (d, 1, $J$ = 6 Hz, C-2 H), 7.74 (dd, 1, $J$ = 6, 8 Hz, C-3 H), 7.17 (d, 1, $J$ = 8 Hz, C-4 H), 3.3–4.0 (1, m, C-5 H), 1.83 (1, dd, $J$ = 9, 13 Hz, C-6 H), 2.45 (1, dd, $J$ = 7, 13 Hz, C-6 H), 1.47 (3, d, $J$ = 7 Hz, C-5 $CH_3$), 1.49 (3, s, C-7 $CH_3$), and 1.60 ppm (3, s, C-7 $CH_3$).

*cis*- **and** *trans*-**2,4-dimethylcyclopentanone** (**9**) was prepared from 3,5-dimethylphenol by the procedure of Klamann and Lache[13] in an overall yield of 54%, bp 92–96° (60 mm).

**2,4,4-Trimethylcyclopentanone** (**11**) was prepared by the method of House[10] from isophorone oxide in 48% yield, bp 69–70° (32 mm).

**2,2,4- and 2,4,4-Trimethylcyclopentanone** (**10 and 11**).—The procedure of Birch and Johnson[11] was followed using dihydroisophorone as a substrate to yield a mixture of ketones **10** and **11** in a yield of 80%, bp 66.5–68° (41 mm). Vpc analysis[14] showed an isomer composition of 59% **11** and 41% **10**.

**3,5,5-Trimethyl-2-hydroxymethylenecyclopentanone** (**12**).—Sodium hydride (57% mineral oil suspension, 6.45 g, 0.155 mol), under nitrogen was washed with hexane and then stirred for 30 min with a mixture of **10** and **11** (33 g, 0.26 mol, 0.15 mol of **11**) in benzene (300 ml). Ethyl formate (24 g, 0.31 mol) and 3 drops of methanol were added and the mixture was stirred for 16 hr at room temperature. The reaction mixture was diluted with ether (200 ml) and extracted with 5% NaOH solution. The combined aqueous extracts were acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The ether extracts were dried ($MgSO_4$), the ether was evaporated,

(14) Vpc column: 10% FFAP, Chromosorb W, 10 ft × 0.125 in., 120°.

and the residue was distilled to yield 15.3 g of 12 (65% based on sodium hydride): bp 75–80° (9 mm); ir ($CCl_4$) 1680 (C=O) and 1610 $cm^{-1}$ (enol double bond); nmr ($CCl_4$) δ 1.05 (s, 3, C-5 Me), 1.1 (s, 3, C-5 Me), 1.15 (d, 3, $J$ = 7 Hz, C-3 Me), 1.3 (dd, 1, $J$ = 12, 10 Hz, C-4 H), 1.95 (dd, 1, $J$ = 12, 7 Hz, C-4 H), 2.5–3.1 (m, 1, C-3 H), 7.1 (d, 1, $J$ = 1.5 Hz, vinyl H), and 12.2 ppm (s, 1, enol OH).

Ketone 11 could be regenerated by heating 12 with aqueous 15% NaOH at reflux for 4 hr. Vpc analysis[14] of the resulting product showed >99% 11.

**3,3,5-Trimethyl-2-hydroxymethylenecyclopentanone.**—Sodium hydride (57% mineral oil suspension, 12.6 g, 0.311 mol), 2,4,4-trimethylcyclopentanone[10] (12.6 g, 0.10 mol), and ethyl formate (22.2 g, 0.31 mol) were allowed to react as described above to yield 10.9 g (71%) of product: bp 57–58° (2.3 mm); ir (thin layer) 1659 (C=O), 1607 $cm^{-1}$ (enol double bond); nmr ($CCl_4$) δ 1.09 (d, 3, $J$ = 7 Hz, C-5 Me), 1.16 (s, 3, C-3 Me), 1.21 (s, 3, C-3 Me), 1.45 (d, 1, $J$ = 11.5 Hz, C-4 H), 1.99 (dd, 1, $J$ = 11.5, 8 Hz, C-4 H), 2.1–2.9 (m, 1, C-5 H), 7.10 (s, 1, vinyl H), and 11.73 ppm (s, 1, enol OH).

**3,5-Dimethyl-2-hydroxymethylenecyclopentanone.**—Sodium hydride (57% mineral oil suspension, 21.5 g, 0.50 mol), 2,4-dimethylcyclopentanone[13] (19 g, 0.17 mol), and ethyl formate (37.8 g, 0.51 mol) in benzene with 3 drops of methanol were allowed to react as described above. Work-up yielded 15 g (63%) of product: bp 100–105° (35 mm); ir ($CCl_4$) 1680 (C=O) and 1612 $cm^{-1}$ (enol double bond); nmr ($CCl_4$) δ 1.10 (d, 3, $J$ = 7 Hz, C-3 or C-5 Me), 1.16 (d, 3, $J$ = 6.5 Hz, C-3 or C-5 Me), 1.4–1.0 (0.5, C-4 H of cis isomer), 1.77 (dd, 1, $J$ = 7, 8 Hz, C-4 H of trans isomer), 2.1–3.1 (m, 2.5, C-3 and C-5 H of cis and trans isomer, C-4 H of cis isomer), 7.04 (d, 0.5, $J$ = 2 Hz, vinyl H), 7.20 (d, 0.5, $J$ = 1.5 Hz, vinyl H of other isomer), and 11.13 ppm (s, 1, enol OH).

**5,7,7-Trimethyl-6,7-dihydro-5*H*-1-pyrindin-2-ol (14).**—Hydroxymethylene ketone (12) (14 g, 91 mmol), cyanoacetamide (10.5 g, 0.12 mol), piperidine (2.8 ml), $H_2O$ (50 ml), and enough ethanol to effect solution were heated together at 40°. Filtration of the reaction mixture after 2.5 and 5 days yielded a white solid, which was recrystallized from ethanol to yield 4.3 g of solid A (22% based on part structure 15): mp 250–265° dec; ir ($CHCl_3$) 3460 (C=O) and 1575 $cm^{-1}$ (double bond); mass spectrum $m/e$ 220 ($M^+$).

Solid A (2.5 g, 13 mmol) and concentrated HCl (10 ml) were heated in a bomb at 185–195° for 5.5 hr. The reaction mixture was diluted with water and neutralized with solid $NaHCO_3$. The resulting solid was collected and recrystallized from ethanol to yield 1.9 g (95%) of 14: mp 188–189°; ir ($CHCl_3$) 1655 (C=O) and 1610 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 1.19 (d, 3, $J$ = 7 Hz, C-5 Me), 1.29 (s, 3, C-7 Me), 1.45 (s, 3, C-7 Me), 1.52 (m, 1, C-6 H), 2.17 (dd, 1, $J$ = 7.5, 12.5 Hz, C-6 H), 2.75–3.35 (m, 1, C-5 H), 6.38 (d, 1, $J$ = 9 Hz, C-3 H), and 7.28 ppm (d, 1, $J$ = 9 Hz, C-4 H).

*Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.65; N, 7.65.

**5,5,7-Trimethyl-6,7-dihydro-5*H*-1-pyrindin-2-ol (13).**—3,3,5-Trimethyl-2-hydroxymethylenecyclopentanone (10 g, 65 mmol), cyanoacetamide (7.1 g, 85 mmol), $H_2O$ (35 ml), and piperidine (2 ml) in ethanol were allowed to react as described above. Filtration of the reaction mixture after 7–14 days yielded a white solid which was recrystallized from ethanol to yield 4.6 g of solid B (31% based on part structure 15): mp 280–283° dec; (Nujol mull) 1661 $cm^{-1}$ (broad); mass spectrum $m/e$ 220.

Solid B (1.0 g, 4.60 mmol) and concentrated HCl (4 ml) were treated as described above to yield after recrystallization from ethanol 710 mg (88%) of 13: mp 163–166°; ir ($CHCl_3$) 3470–2400 (br, NH), 1665 (C=O), 1605 $cm^{-1}$ (C=C); nmr ($CDCl_3$) δ 1.12 (s, 3, C-5 Me), 1.25 (s, 3, C-5 Me), 1.39 (d, 3, J = 6.5 Hz, C-7 Me), 1.53 (m, 1, C-6 H), 2.2 (dd, $J$ = 8, 12.5 Hz, C-6 H), 2.95–3.55 (m, 1, C-7 H), 6.42 (d, 1, $J$ = 9 Hz, C-3 H), and 7.28 ppm (d, 1, $J$ = 9 Hz, C-4 H).

*Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.40; H, 8.48; N, 7.71.

**5,7,7-Trimethyl-6,7-dihydro-5*H*-1-pyrindine (2).**—Dihydropyrindol (14) (1.4 g, 7.9 mmol) and dichlorophenylphosphine oxide were heated for 4 hr at 160–190°. The mixture was diluted with $H_2O$ (50 ml), neutralized with solid $NaHCO_3$, and extracted with ether. After drying ($MgSO_4$), the ether was evaporated to yield 1.25 g of 5,7,7-trimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine (part structure 19) (81%): nmr ($CCl_4$) 1.18 (s, 3, C-7 Me), 1.28 (d, 3, $J$ = 7 Hz, C-5 Me), 1.34 (s, 3, C-7 Me), 1.52 (dd, 1, $J$ = 9, 12.5 Hz, C-6 H), 2.19 (dd, $J$ = 7, 12.5 Hz, C-6 H), 3.1 (m, 1, C-6 H), 6.97 (d, 1, $J$ = 8 Hz, C-3 H), and 7.32 ppm (d, 1, $J$ = 8 Hz, C-4 H).

A mixture of the crude 2-chlorodihydropyrindine (1.2 g, 6.15 mmol), sodium methoxide (440 mg, 6.45 mmol), and Raney nickel (0.2 g) in ethanol (33 ml) was hydrogenated (atmospheric pressure, room temperature). After hydrogen absorption ceased, the catalyst was removed by filtration through Celite, the solvent was evaporated, and the residue was distilled to give 810 mg (82%) of 2: bp 58–59° (1.8 mm); nmr ($CCl_4$) δ 6.91 (dd, 1, $J$ = 5, 7.5 Hz, C-3 H), 7.29 (m, 1, C-4 H), 8.25 ppm (m, 1, C-2 H), and Table I. The picrate of 2, mp 153–155°, showed nmr ($CDCl_3$) δ 7.76 (dd, 1, $J$ = 6, 8 Hz, C-3 H), 8.20 (br d, 1, $J$ = 8 Hz, C-4 H), 8.58 ppm (br d, 1, $J$ = 6 Hz, C-2 H), and Table I. The mixture melting point of picrate 2 and picrate B was 136–146°.

*Anal.* Calcd for $C_{17}H_{18}N_4O_7$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.52; H, 4.54; N, 14.28.

**5,5,7-Trimethyl-6,7-dihydro-5*H*-1-pyrindine (4).**—Dihydropyrindol (13) (1.4 g, 7.9 mmol) and dichlorophenylphosphine oxide (3.5 g, 18 mmol) were treated as described above to yield 1.18 g of 5,5,7-trimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine (part structure 19) (77%): ir ($CCl_4$) 1125 and 1170 $cm^{-1}$ (aryl Cl); nmr ($CCl_4$) δ 1.18 (s, 3, C-5 Me), 1.30 (s, 3, C-5 Me), 1.31 (d, 3, $J$ = 7 Hz, C-7 Me), 1.5 (dd, 1, $J$ = 9.5, 12.5 Hz, C-6 H), 2.2 (dd, 1, $J$ = 7.5, 12.5 Hz, C-6 H), 2.85–3.70 (m, 1, C-7 H), 6.99 (d, 1, $J$ = 8 Hz, C-3 H), and 7.32 ppm (d, 1, $J$ = 8 Hz, C-4 H).

The crude 2-chlorodihydropyrindine (1.18 g, 6.05 mmol) was refluxed for 6 hr with Zn dust (7.75 g, 0.12 mol) and concentrated HCl (29 ml). The mixture was then diluted with $H_2O$, filtered, and made basic. The white, gummy precipitate was removed by filtration and washed several times with ether. The aqueous solution was extracted with ether, the ether extracts were dried ($MgSO_4$), and the ether was evaporated. The residue was distilled to yield 0.42 g of 4: bp 89–91° (4.3 mm); nmr ($CCl_4$) δ 6.90 (dd, 1, $J$ = 5, 8 Hz, C-3 H), 7.27 (br d, 1, $J$ = 8 Hz, C-4 H), 8.24 ppm (br d, 1, $J$ = 5 Hz, C-2 H), and Table I. The picrate of 4, mp 168.5–170.5°, showed nmr ($CDCl_3$) δ 7.71 (dd, 1, $J$ = 6, 8 Hz, C-3 H), 8.08 (dd, 1, $J$ = 2, 8 Hz, C-4 H), 8.61 ppm (dd, 1, $J$ = 2, 6 Hz, C-2 H), and Table I. The mixture melting point of picrate 4 and picrate B was 118–151°.

*Anal.* Calcd for $C_{17}H_{18}N_4O_7$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.58; H, 4.72; N, 13.69.

**3,5-Dimethyl-2-*n*-butylthiomethylenecyclopentanone (16).**—3,5-Dimethyl-2-hydroxymethylenecyclopentanone (7.0 g, 50 mmol), *n*-butylthiol (5.55 g, 61.5 mmol), and *p*-toluenesulfonic acid (16 mg) were refluxed for 4.5 hr in benzene with a water separator. After washing with 10% $NaHCO_3$ and $H_2O$ and drying ($MgSO_4$), the solvent was evaporated and the residue was distilled to yield 9.75 g (92%) of 16: bp 91–93° (0.1 mm); ir ($CHCl_3$) 1690 (C=O), 1580 $cm^{-1}$ (double bond); nmr ($CDCl_3$) δ 0.9–1.3 (6, CMe), 1.3–3.1 (m, 13), and 7.26 ppm (br s, 1, vinyl H).

*Anal.* Calcd for $C_{12}H_{20}OS$: C, 67.89; H, 9.50. Found: C, 68.19; H, 9.21.

***cis*- and *trans*-5,7-Dimethyl-3-cyano-6,7-dihydro-5*H*-1-pyrindin-2-ol (17).**—Thiobutylmethylene ketone 16 (6.5 g, 29 mmol), cyanoacetamide (4.1 g, 49 mmol), and sodium methoxide (2.6 g, 49 mmol) were heated in ethanol at reflux for 3.5 days. The solvent was evaporated and the residue was dissolved in water and acidified with concentrated hydrochloric acid. The solid formed was collected by filtration and recrystallized from ethanol to yield 3.75 g (68%) of 17: mp 256–260° dec; ir ($CHCl_3$) 1655 (C=O), 1587 (double bond), and 2215 $cm^{-1}$ (C≡N); nmr ($CDCl_3$) δ 1.22, 1.28, 1.38, 1.5 (all d, 6 H, $J$ = 7 Hz, C-5 and C-7 Me), 1.15–1.55 (0.6 H, cis $C_6H$), 2.04 (t, 0.8 H, $J$ = 7 Hz, trans $C_6H_2$), 2.4–3.7 (m, 2.6 H), 7.74 (s, 1, C-4 H), 13.0–14.2 ppm (broad, 1, NH).

*Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.56; N, 14.75.

***cis*- and *trans*-5,7-Dimethyl-5*H*-1-pyrindin-2-ol (18).**—Compound 17 (0.6 g, 3 mmol) and concentrated HCl (2.25 ml) were heated as above in a sealed tube at 140–150° for 4 hr. The reaction mixture was diluted with $H_2O$ (20 ml) and neutralized with solid $NaHCO_3$. The resulting solid was collected and crystallized from ethanol to yield 0.45 g (87%) of 18. The isomers could be separated by fractional recrystallization from ethanol: mp (mixture) 195–199°; ir ($CHCl_3$) 1650 (C=O), 1601 $cm^{-1}$ (double bond). The trans isomer showed nmr ($CDCl_3$)

δ 1.17 (d, 3, $J$ = 7 Hz, C-5 or C-7 Me), 1.34 (d, 3, $J$ = 7 Hz, C-5 or C-7 Me), 1.94 (t, 2, $J$ = 7 Hz, C-6 H), 6.40 (d, 1, $J$ = 9.5 Hz, C-4 H), 7.34 (d, 1, $J$ = 9.5 Hz, C-3 H), and 2.9–3.5 ppm (m, 2, C-5 and C-7 H). The cis isomer showed nmr ($CDCl_3$) δ 1.22 (d, 3, $J$ = 7 Hz, C-5 or C-7 Me), 1.42 (d, 3, $J$ = 7 Hz, C-5 or C-7 Me), 1.1–1.55 (1, C-6 H), 2.3–2.9 (m, 1, C-6 H), 2.7–3.4 ppm (m, 2, C-5 and C-6 H).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 8.03; N, 8.61.

*cis*- and *trans*-5,7-Dimethyl-6,7-dihydro-5*H*-1-pyrindine (**3** and **1**).—The mixture of **18** (310 mg, 1.9 mmol) and dichlorophenylphosphine oxide (3 g, 15.4 mmol) was treated as described above. The crude product was filtered through silica gel with chloroform to yield 320 mg (93%) of 5,7-dimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine: nmr ($CDCl_3$) δ 1.00–1.40 (6, C-5 and C-7 $CH_3$), 1.2–1.5 (0.6, cis $C_6$ H), 1.78 (t, 0.8, $J$ = 7 Hz, trans $C_6$ $H_2$), 2.17–2.77 (m, 0.6, cis $C_6$ $H_2$), 2.7–3.5 (m, 2, $C_5$ and $C_7$ H), 6.88 (d, 1, $J$ = 8 Hz, $C_4$ H), 7.25 (d, 2, $J$ = 8 Hz, $C_3$ H); mass spectrum $m/e$ 181 (molecular ion).

A mixture of the 2-chlorodihydropyrindine (300 mg, 1.66 mmol), NaOAc (136 mg, 1.66 mmol), and 5% Pd/C (125 mg) in HOAc was hydrogenated in a Parr apparatus (30 lb, 65°, 3 hr). The mixture was filtered through Celite, concentrated *in vacuo*, diluted with $H_2O$ (30 ml), neutralized with solid $NaHCO_3$, and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to yield 200 mg (76%) of **1** and **3**: nmr ($CCl_4$) δ 7.0 (dd, 1, $J$ = 8, 6 Hz, $C_3$ H), 7.4 (br d, 1, $J$ = 8 Hz, $C_4$ H), 8.37 ppm (br d, 1, $J$ = 6 Hz, $C_2$ H), and Table I. The picrate mixture showed mp 113–124°. The picrate mixture could be separated by fractional recrystallization (EtOH) into the enriched trans and pure cis isomers. The picrate of the cis isomer, mp 125–127°, showed nmr ($CDCl_3$) δ 7.79 (dd, 1, $J$ = 6, 8 Hz, $C_3$ H), 8.13 (d, 1, $J$ = 8 Hz, $C_4$ H), 8.58 ppm (d, 1, $J$ = 6 Hz, $C_2$ H), and Table I. The mixture melting point of picrate **3** and picrate A was 102–120°.

The picrate of the trans isomer (*ca.* 67% pure) showed nmr ($CDCl_3$) δ 7.76 (dd, 1, $J$ = 6, 8 Hz, $C_3$ H), 8.21 (d, 1, $J$ = 8 Hz, $C_4$ H), 8.65 ppm (d, 1, $J$ = 6 Hz, $C_2$ H), and Table I.

*Anal.* Calcd for $C_{16}H_{16}N_4O_7$: C, 51.06; H, 4.29; N, 14.89. Found: C, 51.18; H, 4.38; N, 15.06.

**Registry No.**—**1**, 36358-24-4; 1 picrate, 36358-25-5; **2**, 36358-26-6; 2 picrate, 36358-27-7; **3**, 36358-28-8; **3** picrate, 36358-29-9; **4**, 36411-21-9; **4** picrate, 36358-30-2; **12**, 36358-31-3; **13**, 36358-54-0; **14**, 36358-55-1; **16**, 36358-56-2; *cis*-**17**, 36358-57-3; *trans*-**17**, 36411-24-2; *cis*-**18**, 36358-58-4; *trans*-**18**, 36358-59-5; 5,7-dimethyl-2-chloro-6,7-dihydro-5*H*-1-pyridine (cis), 36358-60-8; 3,3,5-trimethyl-2-hydroxymethylene cyclopentanone, 36358-61-9; *cis*-3,5-dimethyl-2-hydroxymethylenecyclopentanone, 36434-06-7; *trans*-3,5-dimethyl-2-hydroxymethylenecyclopentanone, 36357-91-2; 5,7,7-trimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine, 36357-92-3; 5,5,7-trimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine, 36357-93-4; 5,7-dimethyl-2-chloro-6,7-dihydro-5*H*-1-pyrindine (trans), 36357-94-5.

**Acknowledgment.**—Funds generously provided by the National Science Foundation for the purchase of a 100-MHz nmr spectrometer (GP-6940) and a high-resolution mass spectrograph (GP-8509) are gratefully acknowledged.

# Mesoionic Compounds. XX. Cycloaddition Reactions of Pyrylium Betaines[1]

K. T. POTTS,* A. J. ELLIOTT, AND M. SORM

*Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181*

*Received May 12, 1972*

*anhydro*-3-Hydroxy-2,4,6-triphenylpyrylium hydroxide underwent 1,3-dipolar cycloaddition reactions with a variety of acetylenic and olefinic dipolarophiles, as well as heterocumulenes, forming 1:1 adducts by reaction at the 2,6 positions. Thermolysis of these adducts either resulted in rearrangement to substituted cyclohexadienones or in dissociation to the initial reactants. The adduct from diphenylacetylene was also converted into cycloheptadiene and cycloheptatriene derivatives.

Reports of 1,3-dipolar cycloaddition reactions[2] utilizing carbonyl ylides were, until quite recently, noticeably absent from the literature. The cycloaddition reactions of tetracyanoethylene oxides to olefins, acetylenes, and aromatic compounds,[3] and the thermal condensations of oxiranes in the presence of dipolarophiles,[4] may be interpreted in terms of an intermediate carbonyl ylide **1**. Recently, *cis*- and *trans*-dicyanostilbene oxides were also shown[5] to undergo cycloadditions at temperatures >100° with a variety of acetylenic and olefinic dipolarophiles and, similarly, *cis*- and *trans*-cyanostilbene oxides also underwent cycloadditions. The reactive intermediates in these reactions were carbonyl ylides formed in a conrotatory, electrocyclic ring opening of the oxirane by fission of the C–C bond.[6] The thermal decomposition of $\Delta^3$-1,3,4-oxadiazolines in the presence of dipolarophiles also appears to involve a carbonyl ylide intermediate.[7]

Our interest in cycloaddition reactions in which mesoionic compounds[8a] are utilized as the source of the 1,3 dipole[8b] led us to study whether a suitable mesoionic-type ring system containing a 1,3 dipole of the

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) presented in part at the XXIII IUPAC Congress, Boston, Mass., July 1971.

(2) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).

(3) W. J. Lin, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3651 (1965); W. J. Linn and R. E. Benson, *ibid.*, **87**, 3567 (1965); W. J. Linn, *ibid.*, **87**, 3665 (1965).

(4) (a) E. F. Ullman and J. E. Milks, *ibid.*, **86**, 3814 (1964); E. F. Ullman and W. A. Henderson, Jr., *ibid.*, **88**, 4942 (1966); (b) D. R. Arnold and L. A. Karnischky, *ibid.*, **92**, 1404 (1970); D. R. Arnold and Y. C. Chang, *J. Heterocycl. Chem.*, **8**, 1097 (1971); (c) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1402 (1970); (d) J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **49**, 3444 (1971); (e) J. J. Pommeret and A. Robert, *Tetrahedron*, **27**, 2977 (1971); A. Robert, J. J. Pommeret and A. Foucaud, *Tetrahedron Lett.*, 231 (1971); J. J. Pommeret and A. Robert, *C. R. Acad. Sci., Ser. C*, **272**, 333 (1971); A. Robert, J. J. Pommeret, and A. Foucaud, *ibid.*, **270**, 1739 (1970).

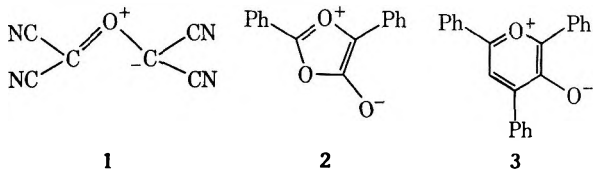
(5) H. Hamberger and R. Huisgen, *Chem. Commun.*, 1190 (1971).

(6) A. Dahman, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.* 1192 (1971).

(7) P. Rajagopalan and B. G. Advani, *Tetrahedron Lett.*, 2689 (1967); R. Hoffman and H. J. Luthardt, *Chem. Ber.*, **101**, 3861 (1968).

(8) (a) W. Baker and W. D. Ollis, *Quart. Rev., Chem. Soc.*, **11**, 15 (1957); for a recent review see M. Ohta and H. Kato in "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, Chapter 4; R. Huisgen in "Aromaticity," Chemical Society Special Publication No. 21, London, 1967, p 51; (b) *e.g.*, K. T. Potts and S. Husain, *J. Org. Chem.*, **36**, 3451 (1971), and references cited therein.

carbonyl ylide type could be devised. In a five-membered ring system *anhydro*-2,5-diphenyl-4-hydroxy-1,3-dioxolium hydroxide (**2**) would contain such a dipole, but this ring system has not yet been synthesized. As



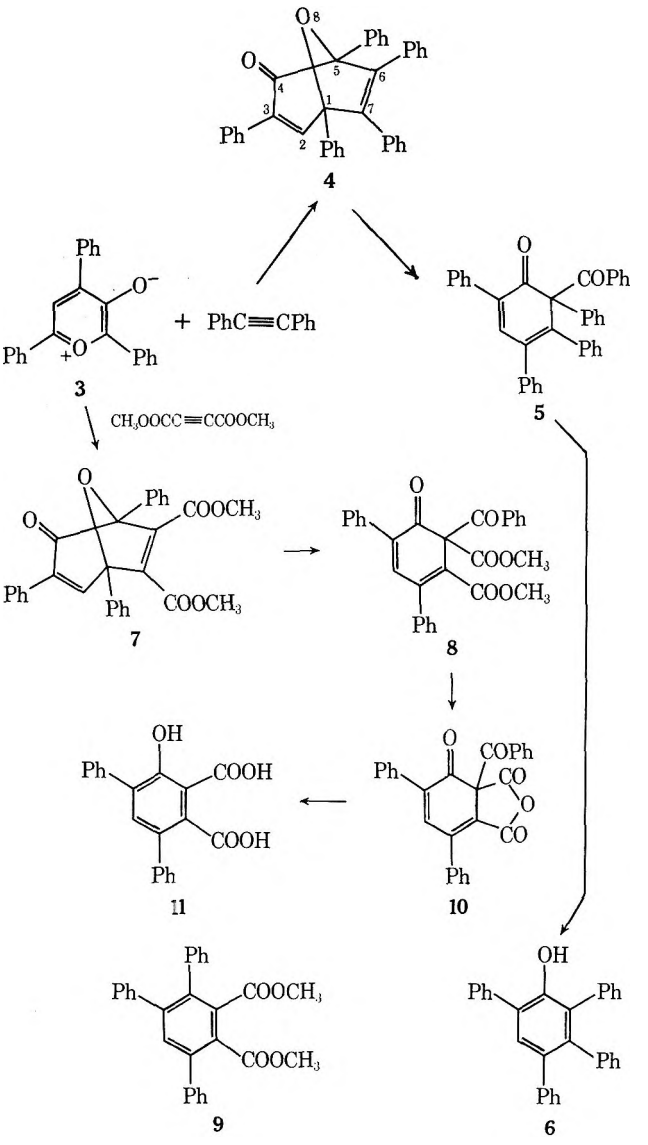
**1** **2** **3**

the oxygen atom at the 3 position may be considered to contribute two electrons to the $6\pi$ position of **2**, its replacement with a vinyl group would be expected to give a product with the desired characteristics of **2**. Such a system is represented by *anhydro*-3-hydroxy-2,4,6-triphenylpyrylium hydroxide (pyrylium betaine) (**3**) and data available in the literature indicate that a study of its cycloaddition reactions would be of great interest.

Other six-membered, heteroaromatic betaines containing 1,3 dipoles of the azomethine ylide type have been shown recently to undergo cycloaddition reactions. With *anhydro*-3-hydroxy-1-methylpyridinium hydroxide, adducts were obtained with olefinic dipolarophiles[9a] but not with acetylenic dipolarophiles[9b] and, with those betaines containing a pyrazine nucleus, 1:1 adducts were obtained with several olefinic and acetylenic dipolarophiles.[9c] The azomethine ylide dipole contained in an isoquinolinium imine has also been shown to react with a variety of olefinic and acetylenic dipolarophiles.[9d]

Studies with pyrylium oxides[10] to date have centered mainly on their photochemical, valence tautomerism characteristics.[4a,11] The benzo[c] analog of **3** was found to give 1:1 adducts with dimethyl acetylenedicarboxylate,[4a] norbornadiene,[4a] and several other olefinic dipolarophiles,[4d] and **3** itself reacted with maleic anhydride to give a 1:1 adduct whose structure, assigned on infrared evidence, is consistent with those reported in this communication.[12] The pyrylium betaine **3** was also shown[13] recently to undergo photochemical or thermal addition of oxygen forming ultimately a ring-opened product, 2-benzoyl-2,4-diphenylbut-3-en-4-olide. A pyrylium betaine intermediate was also postulated to explain the structure of the final, nitrogen-free product from 3,4-diazacyclopentadienone *N*,*N*-dioxide and dimethylacetylenedicarboxylate.[14] These indications of the suitability of the pyrylium betaine **3** as a source of a carbonyl ylide intermediate are amply confirmed by the cycloaddition reactions described below. This system is of additional interest in that it could also conceivably act as a 1,5 dipole in addition to a 1,3 dipole, but no products consistent with a 1,5-dipolar intermediate have been isolated.

Condensation of **3** with diphenylacetylene in boiling benzene yielded a 1:1 adduct, 4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene (**4**); spectral data (Experimental Section) are in accord with this structure and the following transformations provide strong confirmatory evidence. Thermolysis of **4** at 280° (8 mm) resulted in the formation of an isomeric, colorless, crystalline product, $C_{37}H_{26}O_2$, whose spectral characteristics were consistent with those expected for 6-benzoyl-2,4,5,6-tetraphenyl-2,4-cyclohexadienone (**5**). Treatment of **5** with warm potassium hydroxide solution gave 2,3,4,6-tetraphenylphenol (**6**) and benzoic acid.



An analogous 1:1 adduct **7** was formed readily from **3** and dimethyl acetylenedicarboxylate and its spectral characteristics were again consistent with the assigned structure. Moreover, on thermolysis of this adduct, two products were formed, the analogous dimethyl 6-benzoyl-2,4-diphenyl-1-oxo-2,4-cyclohexadiene-5,6-dicarboxylate (**8**) and the related dimethyl 3,4,6-triphenylphthalate (**9**). As anticipated, acid hydrolysis of the ester **8** resulted in formation of the anhydride **10**, which was converted into the phthalic acid **11**.

This mode of addition is a general one with acetylenic dipolarophiles. Dibenzoylacetylene also readily gave the corresponding cycloadduct, 6,7-dibenzoyl-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene (**12**), but in this case reaction with **3** occurred readily at room temperature, a characteristic of the reaction of dibenzoylacetylene with several other 1,3-dipolar sys-

(9) (a) A. R. Katritsky and Y. Takeuchi, *J. Amer. Chem. Soc.*, **92**, 4135 (1970); (b) K. T. Potts, A. J. Elliott, and R. Hsia, unpublished results; (c) J. Honzl, M. Sorm, and V. Hanus, *Tetrahedron*, **26**, 2305 (1970); M. Sorm and J. Honzl, *ibid.*, **28**, 603 (1972); R. Huisgen and H. Mader, *Angew. Chem., Int. Ed. Engl.*, **8**, 604 (1969); (d) J. W. Lown and K. Matsumoto, *J. Org. Chem.*, **36**, 1405 (1971).

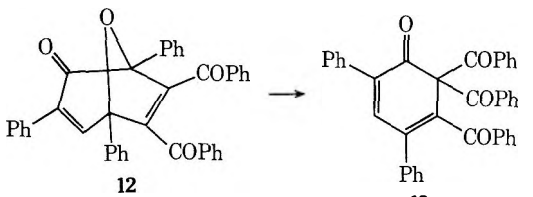
(10) A review on the reaction of pyrylium salts may be found in H. Perst "Oxonium Ions," Verlag Chemie-Academic Press, Weinheim/Bergstr., Germany, 1971.

(11) E. F. Ullman, *J. Amer. Chem. Soc.*, **85**, 3529 (1963); J. M. Dunston and P. Yates, *Tetrahedron Lett.*, 505 (1964).

(12) G. Suld and C. C. Price, *ibid.*, **84**, 2094 (1962).

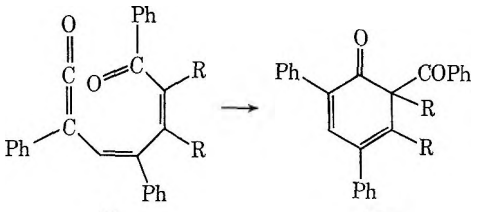
(13) H. H. Wasserman and D. L. Pavia, *Chem. Commun.*, 459 (1970).

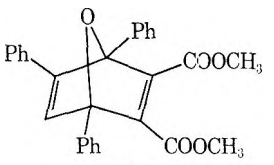
(14) J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36**, 19 (1971).




tems. On thermolysis **12** underwent isomerization to **13**, whose spectral characteristics were consistent with the assigned structure and with those of the analogous compounds described above (see Experimental Section).

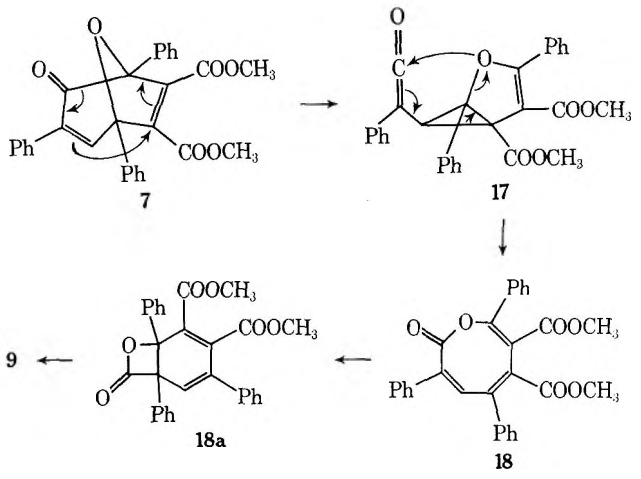
The thermal isomerization of these acetylenic adducts may be readily explained by assuming an initial cleavage of the 4,5 bond with the formation of an intermediate ketene **14**. This may then undergo cyclization to **15** by addition of the diene system to the ketene



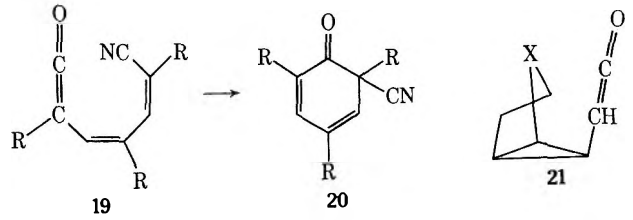




carbonyl group. This ketene intermediate also satisfactorily explains the formation of the second product **9**, isolated in the pyrolysis of the cycloadduct **7**. The dimethylphthalate derivative **9** differs from its precursor by an apparent loss of $CO_2$. Decarbonylation of the ketene **14** with concomitant cyclization to an intermediate bicyclo[2.2.1]heptane system **16** is an unlikely reaction pathway for the formation of **9**, as reactions proceeding with the extrusion of a single atom of oxygen are rare and dehydration processes are usually involved.[15] Such a process is impossible with the substitution pattern of **16**. However, the bond fission leading to the ketene **14** also accounts satisfactorily for the formation of **9**. After fission of the 4,5 bond in **7**, an alternative series of electron shifts would result in the formation of an intermediate **17** which, following attack of the bridge oxygen atom on the carbonyl group, would collapse to **18**. Thermal elimination of $CO_2$ from systems similar to **18** is well authenticated,[16] and probably involves an intermediate such as **18a**.

Several analogies may be found for the rationalizations described above. Thermal cyclization of the diene ketene **19** to the cyclohexa-2,4-dienone **20** has been reported[17a] and cyclopropylketene intermediates **21** have been detected in the photolysis of bicyclic




dienones.[17b] In addition ketene and heterocumulene intermediates have resulted from the thermal[18a] and photochemical[18b] cleavage of several mesoionic systems.




Other experiments also provided support for the original structure assignments made for the primary 1:1 adducts. Reduction of **4** with $H_2/PtO_2$ resulted in the absorption of 1 equiv of hydrogen and the formation of 4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]oct-6-ene (**22**). That the 2,3 double bond had been reduced was evident from the nmr spectrum, which was of the ABX type. Also the change of the carbonyl absorption from 1690 to 1720 $cm^{-1}$ indicated removal of the $\alpha,\beta$ double bond. The dihydro compound was reduced with lithium aluminum hydride to a mixture of epimeric alcohols **23** and an hydrogenolysis product, 1,2,3,4,6-pentaphenylcyclohepta-1,3-diene (**24**). The formation of the latter is not unexpected, as lithium aluminum hydride hydrogenolysis of ether functions has been described.[19] Dehydration of the mixture of epimeric alcohols **23** with *p*-toluenesulfonic acid in hot toluene resulted in complete deoxygenation of the system with the formation of 1,2,3,4,6-pentaphenylcyclohepta-1,3,5-triene (**25**). There was no evidence for the presence of any of the possible norcaradiene valence isomer of **25**, which was also not observed with 1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-triene.[20]

In the above cycloadditions one product only was always isolated from the reaction mixture. The ($4\pi + 2\pi$) cyclization is evidently favored over the alternative ($6\pi + 2\pi$) reaction, which could yield a bicyclo[3.2.1]octane derivative such as **26**. Olefinic dipolarophiles and heterocumulenes also followed a similar reaction pathway, giving products of the type described below.

(15) B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, London, 1967, Chapter 7. This behavior of oxygen is in marked contrast to that of sulfur, which we have found to be readily extruded from primary cycloadducts containing sulfur bridges of this type.

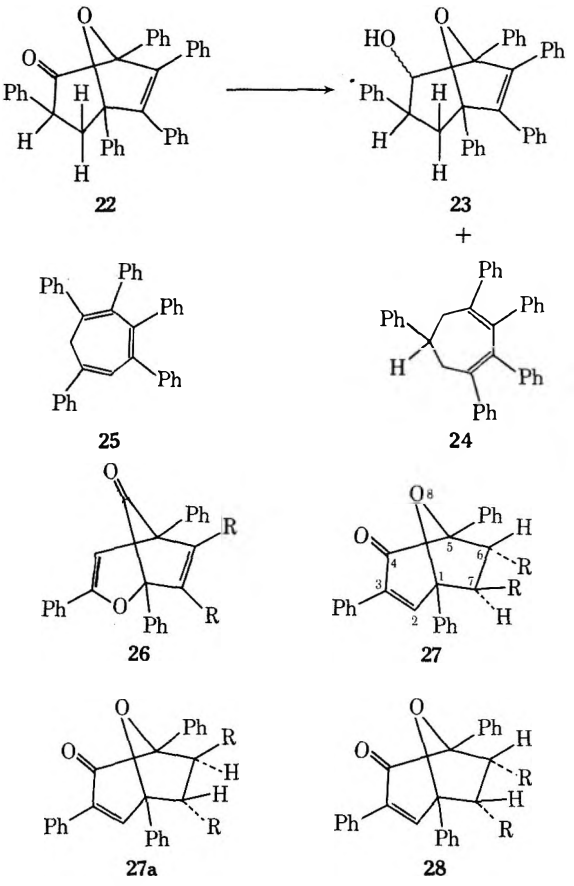
(16) Reference 15, Chapters 3 and 4.

(17) (a) J. D. Hobson, M. M. Al Holly, and J. R. Malpass, *Chem. Commun.*, 764 (1968); (b) O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *J. Amer. Chem. Soc.*, **91**, 6858 (1969); see also T. Sasaki, S. Eguchi, and M. Ohno, *ibid.*, **92**, 3192 (1970).

(18) (a) H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.*, **103**, 2581 (1970); (b) R. M. Moriarty, R. Mukherjee, O. L. Chapman, and D. R. Eckroth, *Tetrahedron Lett.*, 397 (1971).

(19) E. Staude and F. Patat in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, p 65.

(20) M. A. Battiste, *Chem. Ind. (London)*, 550 (1961).




Dimethyl maleate, dimethyl fumarate, fumaronitrile, ethyl vinyl ether, *N*-phenylmaleimide, norbornene, and norbornadiene all formed stable, crystalline 1:1 adducts with the pyrylium betaine **3**. With dimethyl fumarate only one product was isolated (47%) and the intensive tlc analyses of reaction mixtures never showed detectable amounts of isomeric material. The chemical shifts of the 6 and 7 protons suggest structure **27**, R = $COOCH_3$, for this product. Doublets at $\tau$ 5.75 and 5.95 ($J$ = 3.0 Hz) and methyl singlets at $\tau$ 6.27 and 6.87 are consistent with the protons being in a 6-exo,7-endo configuration, this assignment being made on the basis of the chemical shifts of related protons in the adducts described below and on the assumption that, in an oxygen-bridged system of this type, exo protons would be deshielded relative to endo protons. In early stages of this work, it was noticed that these olefinic cycloadducts underwent thermal dissociation to their precursors. It was not surprising, then, that the stereochemically pure fumarate cycloadduct gave rise to an isomeric mixture of products on heating at 127° in anhydrous chlorobenzene for 12 hr. Nmr data indicated that a 3:1 ratio of isomers was produced and the minor product was assigned the 6-endo,7-exo configuration **27a** (R = $COOCH_3$) on the basis of nmr data (Experimental Section).

Fumaronitrile also gave a good yield (75%) of a 1:1 cycloadduct with **3** and this has been assigned structure **27a** (R = CN). In this case the 6 and 7 protons were magnetically equivalent, giving a sharp singlet at $\tau$ 6.03 in the nmr spectrum. When this cycloadduct was heated in chlorobenzene at 127° for 12 hr, it was converted completely into an isomeric product in which the 6 and 7 protons now appeared as two doublets ($J$ = 3.0 Hz) at $\tau$ 6.32 and 6.75. Thus the cycloadduct from **3** and fumaronitrile formed at room temperature most likely had the protons in a 6-endo,7-exo configuration **27a** (R = CN). At reflux temperature a mixture of the two isomeric products was obtained.

A 1:1 cycloadduct was also formed (60%) from dimethyl maleate and **3** in refluxing benzene. The 6 and 7 protons appeared as two doublets at $\tau$ 5.72 and 6.13 with a cis coupling, $J$ = 11.5 Hz. In contrast to the fumarate adduct, the two ester methyl groups were equivalent. *N*-Phenylmaleimide also formed (44%) a 1:1 adduct with $J$ = 9.5 Hz between the 6 and 7 protons which appeared as doublets at $\tau$ 5.70 and 5.93. These chemical shifts indicate an endo configuration for these two adducts, which have been assigned structures **28** (R = $COOCH_3$ and –CONPhCO–, respectively).

The electron-rich, olefinic dipolarophile ethyl vinyl ether and **3** formed a 1:1 cycloadduct (46%). The 6 and 7 protons formed a typical ABX pattern ($J_{AB}$ = 13.0, $J_{AX}$ = 8.75, and $J_{BX}$ = 4.75 Hz) which was consistent with the calculated spectrum. Proton B at $\tau$ 7.32 has to have an endo configuration, which requires the ethoxyl group also to have an endo configuration. Though it cannot be established rigorously, the ether group is most likely at position 6, and the structure of the product is represented by **29**.

The stereochemistry represented in the structures **27–29** is consistent with that recently described for analogous adducts of the benzo analog[4d] of **3**, and for other oxygen-bridged[4d] systems. Experiments aimed at verifying these assignments by chemical methods are currently underway.

Highly strained olefins also reacted with the pyrylium oxide **3**. The 1:1 adduct from norbornene was assigned the exo,exo structure **30** on the basis of its nmr spectrum. A deshielding effect on the syn proton and a corresponding shielding effect on the anti proton of the methylene-bridge protons of norbornene by an oxide bridge has been found in adducts from diphenylisobenzofuran and norbornene ($\tau$ 7.73 and 9.40, respectively),[21] and also in *exo*-1,2-epoxynorbornene ($\tau$ 8.65 and 9.30, respectively).[22] In the nmr spectrum of **30**, the 7-anti proton of the norbornane moiety appeared as one-half of an AB quartet ($J$ = 10.0 Hz), centered at $\tau$ 9.43, while the 7-syn proton was hidden amidst the methylene resonances of the norbornane moiety. There are four possible structures for this adduct (exo,exo, exo,endo, endo,exo, endo,endo), and only the exo,exo product is compatible with this observation. The protons at $C_6$ and $C_7$ of the bicyclo[3.2.1] system were assigned resonances at $\tau$ 7.32 and 7.50 ($J$ = 6.0 Hz), respectively, these chemical shifts clearly requiring these protons to be in the endo configuration.

When excess norbornadiene was treated with **3**, a 1:1 adduct formed in 42% yield and, from five possible isomers (exo,exo, exo,endo, endo,endo, endo,exo, and 1,5 addition), this was assigned structure **31** on the basis of its nmr spectrum and its conversion into **30**. The exo configuration of the adduct was demonstrated by the protons at $C_7$ of the norbornene system appearing as an AB doublet, with the 7-anti proton at $\tau$ 9.20 and the 7-syn proton at $\tau$ 8.12 ($J$ = 9.0 Hz). In

(21) M. P. Cava and F. M. Scheel, *J. Org. Chem.*, **32**, 1304 (1967).
(22) K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 559 (1964).

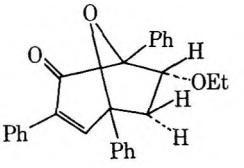
this adduct the norbornene bridgehead protons (at $C_1$ and $C_4$ of the norbornene system) were found as broad singlets at $\tau$ 7.82 and 7.50, and the endo protons at $C_6$ and $C_7$ of the bicyclo[3.2.1]heptane system occurred as an AB doublet ($J$ = 7.0 Hz) at $\tau$ 7.17 and 7.27. Reduction of the adduct **31** with hydrogen and palladium gave the adduct **30**, establishing the close interrelationship of the two adducts.

Reaction of norbornene with 2 equiv of the pyrylium betaine **3** gave a mixture of two bis adducts (41% yield) which has not yielded to chromatographic separation. The nmr spectrum showed 2-methylene protons as a broad singlet at $\tau$ 9.07; no protons were observed at higher fields. The 4-endo protons, *i.e.*, the protons at $C_6$ and $C_7$ of the bicyclo[3.3.2]heptane system, appeared as an $A_2B_2$ quartet ($J$ = 7.0 Hz) centered at $\tau$ 7.50 and 7.30. The most likely structures for these bis adducts are represented by **32** and **33**, respectively, and the nmr data may be rationalized on the basis of these structures. The bridgehead protons in **32** (*i.e.*, those at $C_1$ and $C_4$ of the norbornane system) should appear as two broad singlets ($\tau$ 8.63 and 8.00), whereas the corresponding bridgehead protons in **33** would be anticipated to be a broad singlet. These last protons were assigned to a resonance at $\tau$ 8.30.

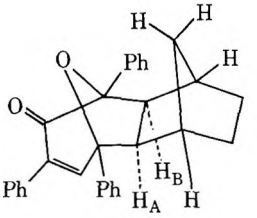
There has been considerable interest of late in the use of three-membered rings as dipolarophiles in cycloadditions. 2,3-Diphenylthiirene 1,1-dioxide and phenyldiazomethane at room temperature have been found to give 3,4,5-triphenylpyrazole (6%), arising from the loss of $SO_2$ from the initial 1,3-dipolar adduct,[23] and various cyclopropane derivatives have also been shown to form interesting adducts in cycloaddition reactions.[24]

The pyrylium betaine **3** and 1,1-diphenylthiirene 1,1-dioxide reacted slowly at room temperature with the loss of $SO_2$, and the presence of diphenylacetylene was detected after a few hours. After 3 days diphenylacetylene, 4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene (**4**), and unchanged pyrylium betaine **3** were present in the reaction mixture. While the adduct **4** might conceivably have been obtained from diphenylacetylene and **3**, it was shown independently that these reactants did not give **4** under these reaction conditions. The adduct **4**, obtained in 25% yield, is thought to arise from the loss of $SO_2$ from the initially formed adduct **34**. In hot benzene solution, only minor reaction occurred between **3** and the thiirene 1,1-dioxide, the latter undergoing complete loss of $SO_2$ in less than 2 hr.

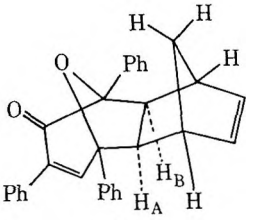
2,3-Diphenylcyclopropenethione has also received considerable attention lately as a dipolarophile[25] and its reaction with 1,3 dipoles offers a convenient method of annelation of a 3-carbon unit. With the pyrylium betaine **3**, a 1:1 adduct (50%) was formed in dry benzene at room temperature over a four-day period. Analytical and spectral data were consistent with the molecular formula represented by structure **35**, 4-oxo-1,3,5,7,8-pentaphenyl-8-thiocarbonyl-9-oxabicyclo[3.3.1]nona-2,6-diene. This assignment can only be regarded as tentative, as the alternative structure **36**



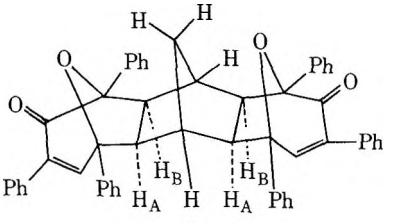
**29**



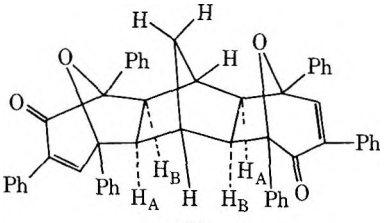
**30**



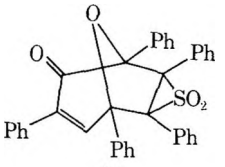
**31**



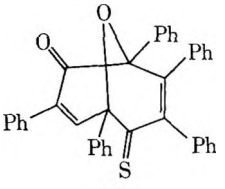
**32**



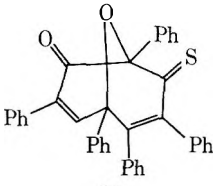
**33**



**34**



**35**



**36**

cannot be excluded on the basis of the available data. However, such a mode of addition is consistent with the known characteristics of the thione and, on the basis of its reactions with other mesoionic systems,[26] structure **35** appears to be the more likely one.

In contrast to the above reaction, diphenylcyclopropenone and **3** gave only 4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene (**4**) arising from addition across the carbon–carbon double bond with subsequent loss of carbon monoxide. Similar behavior has been observed with the benzo[*c*] analog[4d] of **3**. There was no evidence of any other mode of addition which would afford a compound analogous to **36**.

A structural ambiguity also exists with the 1:1 ad-

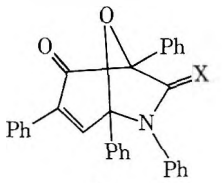
(23) L. A. Carpino, L. V. Mc Adams, R. H. Rynbrandt, and J. W. Spiewak, *J. Amer. Chem. Soc.*, **93**, 476 (1971).

(24) For references see R. Grigg and J. L. Jackson, *J. Chem. Soc. C*, 552 (1970).

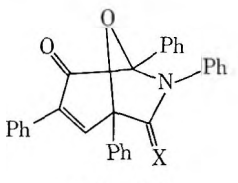
(25) J. W. Lown and K. Matsumoto. *Can. J. Chem.*, **49**, 3119 (1971).

(26) K. T. Potts, J. Baum, and E. Houghton, unpublished results.

ducts formed from **3** and phenyl isocyanate, and also from phenyl isothiocyanate. These adducts, formed in good yield, may be represented by **37** or **38**.



**37**



**38**, X = O, S

An alternative to the use of the pyrylium oxide **3** in these cycloadditions is to carry out the reactions with its perchlorate in the presence of triethylamine. Generation of the pyrylium oxide **3** *in situ* in this fashion has little effect on the yield of purified cycloadduct; it offers considerable experimental convenience over the large-scale preparation of **3** which, unless the conditions described in the Experimental Section are adhered to, often leads to extremely impure products.[27]

In contrast to the adducts with a double bond in the 6,7 positions, the above adducts did not undergo thermal isomerization. Rather, fission of the 5,6 and 7,1 bonds occurred with regeneration of the pyrylium oxide **3** and the dipolarophile. This ready reversion to the initial components was also observed in the mass spectra of these adducts, with a relatively intense ion corresponding to the molecular ion of **3** being observed in all the spectra. It is most likely that this is a thermal process initiated in the ion source. Apart from the diphenylthiocyclopropenone adduct **35** (or **36**), the products described above all gave mass spectra with molecular ions of sufficient intensity to be measured. These established the stoichiometry of the adducts whose fragmentation patterns were consistent with the assigned structures.[28]

## Experimental Section[29]

***anhydro*-3-Hydroxy-2,4,6-triphenylpyrylium Hydroxide**[12] (**3**).—Chalcone (41.6 g) and phenacyl acetate (35.6 g) were dissolved in acetic anhydride (300 ml) and the solution was cooled in an ice bath. Perchloric acid[30] (100 ml, 70%) in acetic acid (50 ml) and acetic anhydride (50 ml) (*Caution: vigorously exothermic*) was then added to the stirred solution during 10–15 min. Stirring was continued for 5 min at 0°, and the reaction mixture was then heated on a steam bath for 10–15 min, after which it was a dark-red color. After cooling (30–60 min) it was poured with stirring into ether (4 l.). A dirty-yellow solid separated which was collected and triturated with acetic acid, giving a bright-yellow product which, on crystallization from acetic acid, separated as canary-yellow plates, mp 230–231°. This perchlorate was dissolved in the minimum amount of dry, cold pyridine and poured onto ice and water. After 2–3 hr the purple solid was collected, washed well with water, and, after drying *in vacuo*, crystallized from acetone from which it separated as purple needles, mp 187–191° (lit[12] mp 193.5–195°).

**Dimethyl 4-Oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate** (**7**).—*anhydro*-3-Hydroxy-2,4,6-triphenylpyrylium hydroxide (**3**) (0.2 g, 0.618 mmol), dimethyl acetylenedicarboxylate (0.2 g, 1.24 mmol), and benzene (10 ml) were refluxed for 1 hr. The solvent was then removed *in vacuo* and the residue was triturated with methanol and finally recrystallized from methanol, giving pale-cream prisms: yield 84%; mp 132–133°; ir (KBr) 3025, 2960, 1720, 1650 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 315 nm (log $\epsilon$ 3.73), 255 (4.00), 217 (4.87); nmr ($CDCl_3$) $\tau$ 6.32 (s, 3, $C_6$ $COOCH_3$), 6.29 (s, 3, $C_7$ $COOCH_3$), 2.67–2.18 (m, 15, aromatic), 2.07 (s, 1, $C_4$ H); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 466 (6).

*Anal.* Calcd for $C_{29}H_{22}C_6$: C, 74.75; H, 4.79. Found: C, 74.62; H, 4.75.

**4-Oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene** (**4**) was obtained from **3** and diphenylacetylene in refluxing benzene over 50 hr. The crude product was triturated with ether and recrystallized from ethanol, separating as pale-yellow prisms: yield 62%; mp 187–189°; ir (KBr) 3025, 3060, 1690 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 315 nm (log $\epsilon$ 3.43), 277 (3.97), 225 (4.52); nmr ($CDCl_3$) $\tau$ 3.32–2.30 (m, 25, aromatic), 2.0 (s, 1, $C_2$ H); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 502 (13).

*Anal.* Calcd for $C_{37}H_{26}O_2$: C 88.42; H, 5.21. Found: C, 88.19; H, 5.22.

Similarly, **6,7-dibenzoyl-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene** (**12**) was obtained when the pyrylium betaine **3** (1.61 g, 0.5 mmol), dibenzoylacetylene (1.17 g, 0.5 mmol), and dry benzene (100 ml) were stirred together for 30 min at room temperature. The solvent was removed *in vacuo* and the residue was chromatographed on Florisil using benzene as eluent. The product separated as yellow needles from hexane: yield 57%; mp 84–85°; ir (KBr) 3075, 3045, 2960, 2940, 1710, 1660 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 315 nm (log $\epsilon$ 3.35), 267 sh (3.83), 230 (4.29); nmr ($CDCl_3$) $\tau$ 3.00–2.00 (m, 25, aromatic), 1.13 (s, 1, $C_2$ H); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 558 (5).

*Anal.* Calcd for $C_{39}H_{26}C_4$: C, 83.85; H, 4.69. Found: C, 83.46; H, 4.99.

**Thermal Isomerization of 4-Oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene** (**4**).—The above adduct (0.502 g, 0.001 mol) was heated at 280° for 1 hr in a vacuum (*ca.* 8 mm) and the product, after cooling, was chromatographed on silica gel using petroleum ether (bp 30–60°)–benzene (1:1) as eluent. Crystallization from ethanol afforded **6-benzoyl-2,4,5,6-tetraphenyl-2,4-cyclohexadienone** (**5**) as colorless needles: yield 60%; mp 192–194°; ir (KBr) 3050, 1735 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 260 nm (log $\epsilon$ 4.58), 243 (4.74); nmr ($CDCl_3$) $\tau$ 2.2–3.1 (m, aromatic); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 502 (15).

*Anal.* Calcd for $C_{37}H_{26}O_2$: C, 88.42; H, 5.21. Found: C, 88.25; H, 5.13.

**Hydrolysis of 6-Benzoyl-2,4,5,6-tetraphenyl-2,4-cyclohexadienone** (**5**).—The dienone (0.15 g, 0.29 mol), KOH (0.15 g), ethanol (20 ml), and water (3 ml) were refluxed for 3 hr. The cold mixture was acidified with dilute HCl and the solvent was then evaporated *in vacuo*. The residue was washed with water, dried, and recrystallized from cyclohexane, giving colorless prisms of 2,4,5,6-tetraphenylphenol (**6**): yield 76%; mp 244–246°; ir (KBr) 3540, 3040 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 295 nm sh (log $\epsilon$ 4.07), 265 sh (4.58), 247 (4.82), 204 (4.94); nmr ($CDCl_3$) $\tau$ 4.75 (s, 1, OH, exchanged with $D_2O$), 3.1–2.2 (m, 21, aromatic); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 398 (100).

*Anal.* Calcd for $C_{30}H_{22}O$: C, 90.45; H, 5.56. Found: C, 90.16; H, 5.62.

**Thermal Isomerization of Dimethyl 4-Oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate** (**7**).—The adduct **7** (0.35 g, 0.785 mmol) was heated at 190° for 2 hr under vacuum (*ca.* 8 mm) and the product was then chromatographed on silica gel using benzene–ether (95:5) as eluent. The first fraction, after recrystallization from methanol, afforded colorless prisms of **dimethyl 3,4,6-triphenylphthalate** (**9**): yield 13%; mp 205–206°; ir (KBr) 3040, 2960, 1730, 1720 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 247 nm (log $\epsilon$ 4.64), 204 (4.72); nmr ($CDCl_3$) $\tau$ 6.50 (s, 3, $C_2$ $COOCH_3$), 6.40 (s, 3, $C_1$ $COOCH_3$), 2.89–2.48 (m, 16, aromatic); mass spectrum *m/e* (rel intensity) M$\cdot^+$ 422 (100).

*Anal.* Calcd for $C_{28}H_{22}O_4$: C, 79.56; H, 5.28. Found: C, 79.57; H, 5.27.

The second fraction crystallized from methanol as colorless needles of **dimethyl 6-benzoyl-2,4-diphenyl-2,4-cyclohexadien-1-one-5,6-dicarboxylate** (**8**): yield 43%; mp 189–190°; ir

(27) If the crude pyrylium oxide **3** melts above 140°, it may be used without extensive purification and will yield reasonable adducts.

(28) The mass spectra were all determined utilizing the direct inlet probe of the Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV, with a source temperature of *ca.* 150°.

(29) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 421 and 331 spectrophotometers; ultraviolet spectra, Cary 14 spectrophotometer; nmr spectra, Varian A-60 and T-60 spectrometers, using TMS as internal standard. Melting points were determined in capillaries and all evaporations were carried out using a Rotovap apparatus. Microanalyses were performed by Instranal Laboratories, Inc., Rensselaer, N. Y.

(30) Use of perchloric acid below 70% strength will prevent separation of the perchlorate when the reaction mixture is added to ether. This perchlorate must be bright yellow and reasonably pure for effective conversion into the pyrylium oxide **3**. The latter should be collected using gravity filtration only.

(KBr) 3040, 2960 1735 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 235 nm (log $\epsilon$ 4.83), 200 (5.07); nmr ($CDCl_3$) $\tau$ 6.40 (s, 3, $C_5$ $COOCH_3$), 6.09 (s, 3, $C_5$ $COOCH_3$), 2.90–2.26 (m, 15, aromatic), 1.84 (s, 1, $C_3$ H); mass spectrum *m/e* (rel intensity) M·$^+$ 466 (14).

*Anal.* Calcd for $C_{29}H_{22}O_6$: C, 74.80; H, 4.74 Found: C, 74.78; H, 4.79.

**6-Benzoyl-2,4-diphenyl-2,4-cyclohexadiene-2,6-dicarboxylic Acid Anhydride** (10).—Dimethyl 6-benzoyl-2,4-diphenyl-2,4-cyclohexadien-1-one-5,6-dicarboxylate (8) (0.4 g), acetic acid (3.5 ml), and $H_2SO_4$ (0.35 ml) were refluxed for 3 hr. After cooling, the reaction mixture was treated with water, and the solid which precipitated was collected, washed with water, and dried *in vacuo*. Crystallization from ether gave colorless prisms of the anhydride: yield 100%; mp 220°); ir (KBr) 3050, 2875, 1850, 1790, 1750, 1730 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 302 nm (log $\epsilon$ 4.25), 244 sh (4.80); nmr ($CDCl_3$) $\tau$ 2.8–2.2 (m, 15, aromatic), 1.9 (s, 1, $C_3$ H); mass spectrum *m/e* (rel intensity) M·$^+$ 420 (5).

*Anal.* Calcd for $C_{27}H_{16}O_5$: C, 77.14; H, 3.84. Found: C, 76.69; H, 3.98.

**3-Hydroxy-4,6-diphenylphthalic Acid** (11).—The above anhydride (0.1 g) was refluxed for 2 hr with excess alcoholic NaOH. The solvent was removed *in vacuo* and the residue was treated with dilute HCl. The solid precipitate was extracted with ether, and the ether solution was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from aqueous ethanol affording colorless prisms: yield 100%; mp 231–232°; ir (KBr) 3509, 3200–2300, 1730, 1685 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 287 sh nm (log $\epsilon$ 3.56), 257 sh (4.19), 241 (4.49); mass spectrum *m/e* (rel intensity) 316 (37) (M·$^+$ of anhydride), 272 (12), 271 (12), 250 (20), 249 (100), 244 (12), 217 (18), 147 (23), 146 (25), 118 (22), 105 (45), 104 (50), 93 (14), 77 (54).

*Anal.* Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.43; H, 4.43.

**Thermal Isomerization of 6,7-Dibenzoyl-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene** (12).—The adduct 12 (2.0 g) was heated at 190° for 1 hr under vacuum (*ca.* 1 mm) and the product, after cooling, was chromatographed on silica gel using benzene as eluent. Crystallization from hexane–benzene afforded **2,4-diphenyl-5,6,6-tribenzoyl-2,4-cyclohexadienone** (13) as colorless needles: yield 29%; mp 194–195°; ir (KBr) 3060, 2920, 2850, 1750, 1660 cm$^{-1}$; $\lambda_{max}^{MeOH}$ 255 nm (log $\epsilon$ 4.69), 202 (5.17); nmr ($CDCl_3$) $\tau$ 3.0–2.0 (m, aromatic); mass spectrum (rel intensity) M·$^+$ 558 (9).

*Anal.* Calcd for $C_{39}H_{26}O_4$: C, 83.85; H, 4.69. Found: C, 83.45; H, 4.61.

**Catalytic Hydrogenation of 4-Oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene** (4).—The diene 4 (0.65 g, 1.3 mmol) dissolved in THF (20 ml) and a catalytic amount of $PtO_2$ were shaken with hydrogen (30 psi) for 6 hr. The catalyst was filtered, the solvent was evaporated, and the residue was recrystallized from ethanol, affording colorless prisms of **4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]oct-6-ene** (22): yield 76%; mp 210–212°; ir (KBr) 3060, 3030, 2945, 2865, 1720 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 265 sh nm (log $\epsilon$ 3.70), 240 (4.00), 292–335 (end absorption); nmr ($CDCl_3$) $\tau$ 7.18 (qt, 1, $H_2$ exo, $J_{2\text{-exo},2\text{-endo}}$ = 14 Hz; $J_{2\text{-exo},3\text{-endo}}$ = 10 Hz); 6.72 (qt, 1, $H_2$ endo; $J_{2\text{-endo},3\text{-endo}}$ = 9 Hz), 5.38 (qt, 1, $H_3$ endo), 3.20–2.32 (m, 25, aromatic); mass spectrum *m/e* (rel intensity) 374 (32), 372 (100), 207 (11), 105 (25), 77 (13).

*Anal.* Calcd for $C_{37}H_{28}O_2$: C, 88.01; H, 5.60. Found: C, 87.87; H, 5.64.

**Lithium Aluminum Hydride Reduction of 4-Oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]oct-6-ene** (22).—The above ketone 22 (0.7 g, 1.39 mmol), $LiAlH_4$ (0.15 g, 4.0 mmol), and THF (20 ml) were refluxed under $N_2$ for 5 days. The reaction mixture was cooled, treated with water, and filtered. The filtrate was evaporated *in vacuo* and the solid residue was chromatographed on silica gel. The petroleum ether (bp 60–80°) effluent was recrystallized from acetonitrile, giving colorless prisms of **1,2,3,4,6-pentaphenylcyclohepta-1,3-diene** (24): yield 30%; mp 198–200°; ir (KBr) 3060, 3030, 2950, 2925 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 295 sh nm (log $\epsilon$ 4.15), 268 (4.24), 222 (4.21); nmr ($CDCl_3$) $\tau$ 6.82 (d, 4, $CH_2$), 6.08 (quintet, 1, CH, $J_{CH_2,CH}$ = 6.5 Hz), 3.13–2.80 (m, 25, aromatic); mass spectrum *m/e* (rel intensity) M·$^+$ 474 (45).

*Anal.* Calcd for $C_{37}H_{30}$: C, 93.63; H, 6.37. Found: C, 93.38; H, 6.45.

The petroleum ether–benzene (7:3) effluent, after crystallization from acetonitrile, gave colorless plates of **2-hydroxy-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]oct-6-ene** (23): yield 22%; mp 227–229°; ir (KBr) 3580, 3065, 3040, 2900 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 298 nm (log $\epsilon$ 3.82), 244 (3.82); mass spectrum *m/e* (rel intensity) M·$^+$ 506 (20).

*Anal.* Calcd for $C_{37}H_{30}O_2$: C, 87.55; H, 5.94. Found: C, 87.43; H, 6.00.

**Formation of 1,3,4,5,6-Pentaphenyl-1,3,5-cycloheptatriene** (25).—2-Hydroxy-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]oct-6-ene (23) (0.506 g, 0.001 mol), *p*-toluenesulfonic acid (0.191 g, 0.001 mol), and toluene (20 ml) were refluxed for 6 hr. After cooling, *p*-toluenesulfonic acid separated and was filtered. The filtrate was washed with $NaHCO_3$ (5% solution), dried ($CaCl_2$), and evaporated *in vacuo*. The residue was recrystallized from acetonitrile and from cyclohexane, affording colorless prisms: yield 85%; mp 218–220°; ir (KBr) 3030, 2900, 1600, 1500, 1490 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 373 sh nm (log $\epsilon$ 4.08), 358 (4.26), 259 (4.45), 219 sh (4.50), 208 sh (4.62), 202 (4.66); nmr ($CDCl_3$) $\tau$ 8.58 (s, 2, $CH_2$), 4.89 (s, 1, CH), 3.5–2.0 (m, 25, aromatic); mass spectrum *m/e* (rel intensity) M·$^+$ 472 (10).

*Anal.* Calcd for $C_{37}H_{28}$: C, 94.01; H, 5.97. Found: C, 94.19; H, 5.55.

**Reaction of 3 with Dimethyl Fumarate.**—The pyrylium betaine 3 (1.62 g, 0.5 mmol), dimethyl fumarate (0.72 g, 0.5 mmol), and dry benzene were heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (benzene) and crystallized from cyclohexane to give colorless plates of **6,7-dicarbomethoxy-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]oct-2-ene** (27, R = $COOCH_3$): yield 47%; mp 184°; ir (KBr) 3075, 3050, 3020, 2945, 1730, 1720, 1710 cm$^{-1}$; nmr ($CDCl_3$) $\tau$ 6.87 (s, 3, $COOCH_3$), 6.27 (s, 3, $COOCH_3$), 5.95 (d, 1, $J$ = 3.0 Hz), 5.75 (d, 1, $J$ = 3.0 Hz), 2.77–2.00 (m, 16, aromatic); $\lambda_{max}^{CH_3OH}$ 255 nm (log $\epsilon$ 3.93), 216 sh (4.70); mass spectrum *m/e* (rel intensity) M·$^+$ 468 (2).

*Anal.* Calcd for $C_{29}H_{24}O_6$: C, 74.34; H, 5.16. Found: C, 74.24; H, 5.22.

Similarly, the pyrylium betaine 3 and dimethyl maleate on reflux for 4 hr in benzene and reaction work-up as above gave **6,7-dicarbomethoxy-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]oct-2-ene** (28, R = $COOCH_3$) as colorless plates from cyclohexane: yield 60%; mp 176–178°; ir (KBr) 3075, 3050, 3010, 2950, 1745, 1700 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 255 nm (log $\epsilon$ 3.87), 216 sh (4.64); nmr ($CDCl_3$) $\tau$ 6.23 (s, 6, 2 $COOCH_3$), 6.13 (d, 1, $J$ = 11.5 Hz), 5.72 (d, 1, $J$ = 11.5 Hz), 2.67–2.20 (m, 16, aromatic), 2.07 (s, 1, $C_2$ H); mass spectrum *m/e* (rel intensity) M·$^+$ 468 (5).

*Anal.* Calcd for $C_{29}H_{24}O_6$: C, 74.34; H, 5.16. Found: C, 74.43; H, 5.08.

**6,7-Dicyano-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]oct-2-ene** (27, R = CN) was obtained from equivalent amounts of the pyrylium betaine 3 and fumaronitrile in benzene at room temperature. After 6 hr, the solvent was removed *in vacuo* and methanol was added to the liquid residue, causing it to crystallize. Crystallization from cyclohexane gave colorless prisms: yield 75%; mp 217–218°; ir (KBr) 3075, 3045, 2945, 2260, 1710 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 285 nm (log $\epsilon$ 3.80), 215 sh (4.58); nmr ($CDCl_3$) $\tau$ 6.03 (s, 2, $C_6$ + $C_7$), 2.80–2.33 (m, 16, aromatic); mass spectrum *m/e* (rel intensity) M·$^+$ 402 (6).

*Anal.* Calcd for $C_{27}H_{18}N_2O_2$: C, 80.58; H, 4.51; N, 6.96. Found: C, 80.36; H, 4.49; N, 6.85.

**6-Ethoxy-4-oxo-1,3,5-triphenyl-8-oxabicyclo[3.2.1]oct-2-ene** (29).—The pyrylium betaine 3 (1.62 g, 0.5 mmol), ethyl vinyl ether (5 ml), and dry benzene (100 ml) were heated under reflux for 6 hr. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel in benzene. Crystallization from hexane gave colorless prisms: yield 46%; mp 117–118°; ir (KBr) 3075, 3045, 2975, 2890, 1690 cm$^{-1}$; $\lambda_{max}^{CH_3OH}$ 267 nm (log $\epsilon$ 3.76), 215 sh (4.41); nmr ($CDCl_3$) $\tau$ 8.60 (t, 3, $J$ = 7.0 Hz), 6.30 (qt, 2, $J$ = 7.0 Hz), 7.60–6.80 (m, 2, $C_7$ H, AB portion of ABX), 5.80–5.40 (m, $C_6$ H, X portion of ABX; ABX calcd $\nu_A$ $\tau$ 6.93, $\nu_B$ 7.32, $\nu_X$ 5.53, $J_{AB}$ = 13.0, $J_{AX}$ = 8.75, $J_{BX}$ = 4.75 Hz), 3.0–2.0 (m, 16, aromatic); mass spectrum *m/e* (rel intensity) M·$^+$ 396 (10).

*Anal.* Calcd for $C_{27}H_{24}O$: C, 81.79; H, 6.10. Found: C, 81.60; H, 6.13.

**Reaction of 3 with Norbornene.**—The pyrylium betaine 3 (0.972 g, 0.003 mol) and norbornene (0.31 g, 0.0033 mol) in toluene (10 ml) were refluxed for 30 min. The solvent was removed *in vacuo* and the semisolid residue was chromatographed on silica gel in benzene. Crystallization of the initial fraction from cyclohexane afforded colorless needles of the adduct **30**: yield 32%; mp 202–203°; ir (KBr) 3075, 3045, 2975, 2945, 2885, 1700 cm$^{-1}$; nmr ($CDCl_3$) $\tau$ 9.43 (d, 1, $C_7$ anti H, $J$ = 10.0

Hz), 8.4–9.2 (m, 5, $CH_2$ + $C_7$ syn H), 8.25 (broad s, 1, $C_{1(4)}$ H), 7.95 (broad s, 1, $C_{1(4)}$ H), 7.54 (d, 1, $H_A$), 7.32 (d, 1, $H_B$, $J_{AB}$ = 7.0 Hz), 2.0–3.0 (m, 16, aromatic); $\lambda_{max}^{CH_3OH}$ 268 nm (log $\epsilon$ 3.10), 218 sh (3.80); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 418 (82).

*Anal.* Calcd for $C_{30}H_{26}O_2$: C, 86.20; H, 6.26. Found: C, 85.94; H, 6.31.

Similarly, the pyrylium betaine **3** and a tenfold excess of norbornadiene afforded the 1:1 adduct **31**, which separated as colorless needles from cyclohexane: yield 42%; mp 157–158°; ir (KBr) 3075, 3045, 2960, 2940, 1690 $cm^{-1}$; $\lambda_{max}^{CH_3OH}$ 270 nm (log $\epsilon$ 3.54), 218 sh (4.28); nmr ($CDCl_3$) $\tau$ 9.20 (d, 1, $C_7$ anti H, $J$ = 9.0 Hz), 8.12 (d, 1, $C_7$ syn H, $J$ = 9.0 Hz), 7.82 (broad s, 1, $C_{1(4)}$ H), 7.50 (broad s, 1, $C_{1(4)}$ H), 7.27 (d, 1, $H_A$), 7.17 (d, 1, $H_B$, $J_{AB}$ = 7.0 Hz), 3.92 (broad m, 2, olefinic), 3.0–2.0 (m, 16, aromatic); mass spectrum *m/e* (rel intensity) 416 (2).

*Anal.* Calcd for $C_{30}H_{24}O_2$: C, 86.51; H, 5.81. Found: C, 86.12; H, 5.84.

Catalytic reduction of a sample of the above 1:1 adduct (**31**) in ethyl acetate solution (10% palladium on charcoal catalyst) afforded a product identical[31] with that prepared from norbornene.

**The 2:1 Adduct with Norbornadiene (32 and 33).**—The pyrylium betaine **3** (3.24 g, 0.01 mol), norbornadiene (0.45 g, 0.005 mol), and dry benzene (120 ml) were refluxed for 2 hr. Removal of the solvent *in vacuo* gave a semisolid residue which crystallized on the addition of methanol. Crystallization from *n*-butyl alcohol gave the bis adducts **32** and **33** as colorless needles: yield 41%; mp 333–335°; ir (KBr) 3075, 3045, 2940, 1710 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ 9.07 (broad s, 2, $C_7$ H), 8.63, 8.30, 8.00 (3 broad s, 2, $C_{1(4)}$ H), 7.50 (d, 2, $H_A$), 7.30 (d, 2, $H_B$, $J_{AB}$ = 7.0 Hz), 2.9–2.4 (m, 30, aromatic); $\lambda_{max}^{CH_3OH}$ 270 nm (log $\epsilon$ 4.06), 215 sh (4.68); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 740 (4).

*Anal.* Calcd for $C_{53}H_{40}N_4$: C, 85.91; H, 5.44. Found: C, 85.67; H, 5.44.

**Reaction of 3 with 2,3-Diphenylthirene 1,1-Dioxide.**—The pyrylium betaine **3** (1.62 g, 0.05 mmol), 2,3-diphenylthiirene dioxide (1.81 g, 0.75 mmol), and dry benzene (50 ml) were stirred together at room temprature for 3 days. The solvent was removed *in vacuo* and the pale yellow solid was crystallized twice from methanol, giving pale yellow prisms of **4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene**[31] (**4**), yield 25%, mp 186–189°.

**Reaction of 3 with 2,3-Diphenylcyclopropenethione.**—Equivalent amounts of the pyrylium betaine **3** and 2,3-diphenylcyclopropenethione were stirred together at room temperature in dry benzene. Chromatography on silica gel (benzene) followed by recrystallization from ethyl acetate afforded **4-oxo-1,3,5,6,7-pentaphenyl-8-thioxo-9-oxabicyclo[3.3.1]nona-2,6-diene** (**35**) as pale yellow needles: mp 228°; ir (KBr) 3075, 3045, 2940, 1695 $cm^{-1}$; $\lambda_{max}^{CH_3OH}$ 335 nm (log $\epsilon$ 4.16), 280 sh (4.21), 222 (4.66); nmr ($CDCl_3$) $\tau$ 3.73 (s, 1, $C_2$ H), 2.80–2.17 (m, 25, aromatic); mass spectrum *m/e* (rel intensity) 441 (88), 105 (100).

*Anal.* Calcd for $C_{38}H_{26}O_2S$: C, 83.50; H, 4.79. Found: C, 82.99; H, 4.68.

**4,6-Dioxo-1,3,5,7-tetraphenyl-7-aza-8-oxabicyclo[3.2.1]oct-2-ene** (**37**, **X** = **O**).—The pyrylium betaine **3** (0.2 g, 0.618 mmol), phenyl isocyanate (0.081 g, 0.68 mmol), and dry benzene (12 ml) were refluxed for 5 hr. After removal of the solvent *in vacuo*, a small volume of methanol was added to the liquid residue, causing it to crystallize. Crystallization from methanol afforded yellow prisms: yield 80%; mp 178–179°; ir (KBr) 3040, 1760, 1630, 1600, 1580, 1500 $cm^{-1}$; $\lambda_{max}^{CH_3OH}$ 345 nm (log $\epsilon$ 3.91), 265 (4.31), 216 sh (4.37); nmr ($CDCl_3$) $\tau$ 3.17–2.10 (m, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 443 (2).

*Anal.* Calcd for $C_{30}H_{21}NO_3$: C, 81.35; H, 4.78; N, 3.16. Found: C, 81.32; H, 4.77; N, 3.09.

Similarly **4-oxo-1,2,5,7-tetraphenyl-6-thioxo-7-aza-8-oxabicyclo[3.2.1]oct-2-ene** (**37**, **X** = **S**) prepared from **3** and phenyl isothiocyanate crystallized from methanol as yellow prisms: yield 75%; mp 194–195°; ir (KBr) 3050, 1640, 1600, 1580, 1500 $cm^{-1}$; $\lambda_{max}^{CH_3OH}$ 348 nm (log $\epsilon$ 3.46), 272 (4.01), 218 sh (4.19); nmr ($CDCl_3$) $\tau$ 3.17–2.10 (m, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 459 (9).

*Anal.* Calcd for $C_{30}H_{21}NO_2S$: C, 78.49; H, 4.60; N, 3.03. Found: C, 78.33; H, 4.62; N, 2.97.

The adduct formed from *N*-phenylmaleimide and **3** under the above conditions also crystallized from methanol, and cyclohexane, separating as colorless, irregular prisms: yield 44%; mp 203–205°; ir (KBr) 3040, 2930, 1700, 1600, 1500 $cm^{-1}$; $\lambda_{max}^{CH_3OH}$ 258 nm (log $\epsilon$ 3.76), 216 sh (4.52); nmr ($CDCl_3$) $\tau$ 5.93 (d, 1, $C_7$ exo H, $J$ = 9.5 Hz), 5.70 (d, 1, $C_6$ exo H, $J$ = 9.5 Hz), 3.07–1.83 (m, 21, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 497 (13).

*Anal.* Calcd for $C_{33}H_{23}NO_4$: C, 79.66; H, 4.66; N, 2.82. Found: C, 79.52; H, 4.76; N, 2.65.

**Thermal Isomerization of the Dimethyl Fumarate Adduct** (**27**, **R** = **COOCH$_3$**).—The adduct **27** in anhydrous chlorobenzene was heated in a sealed nmr tube at 127° for 12 hr. The red coloration which developed during this period was lost on cooling. The nmr (before heating) showed $\tau$ 6.23 (d, 1, $J$ = 3.0 Hz), 5.95 (d, 1, $J$ = 3.0 Hz), 7.40 (s, 3), 6.90 (s, 3); after heating, in addition to the above, new peaks appeared at $\tau$ 6.50 (d, 1, $J$ = 3.0 Hz), 6.05 (d, 1, $J$ = 3.0 Hz), 7.25 (s, 3), and 6.90 (s, 3); isomer ratio by integration was shown to be 3:1.

**Thermal Isomerization of the Fumaronitrile Adduct** (**27a**, **R** = **CN**).—The adduct was heated as above and, after 12 hr, all the initial product had isomerized: nmr (before heating) ($CDCl_3$) $\tau$ 6.03 (s, 2); after heating ($C_6H_5Cl$) $\tau$ 6.75 (d, 1, $J$ = 3.0 Hz), 6.32 (d, 1, $J$ = 3.0 Hz).

**Reaction of 3 with 2,3-Diphenylcyclopropenone.**—Equivalent amounts of the pyrylium betaine **3** and 2,3-diphenylcyclopropenone were boiled under reflux in dry toluene for 6 hr. Chromatography on silica gel (benzene) followed by crystallization from methanol afforded pale yellow prisms of 4-oxo-1,3,5,6,7-pentaphenyl-8-oxabicyclo[3.2.1]octa-2,6-diene[31] (**4**), yield 61%, mp 186–189°.

**Registry No.**—**3**, 31994-72-6; **4**, 35740-90-0; **5**, 35867-16-4; **6**, 913-58-6; **7**, 35740-92-2; **8**, 35740-93-3; **9**, 35740-94-4; **10**, 35740-95-5; **11**, 35740-96-6; **12**, 35740-97-7; **13**, 35740-98-8; **22**, 35740-99-9; **23** (*exo*-OH), 35741-00-5; **23** (*endo*-OH), 35741-01-6; **24**, 35741-02-7; **25**, 35741-03-8; **27** (R = $COOCH_3$), 35741-04-9; **27** (R = CN), 35820-74-7; **27a** (R = $COOCH_3$), 35741-05-0; **27a** (R = CN), 35741-06-1; **28** (R = $COOCH_3$), 35741-07-2; **28** (R = CONPhCO), 35741-08-3; **29**, 35741-09-4; **30**, 35741-10-7; **31**, 35820-75-8; **32**, 35741-11-8; **33**, 35741-12-9; **35**, 35741-13-0; **37** (X = O), 35741-14-1; **37** (X = S), 35741-15-2; **38** (X = O), 35741-16-3; **38** (X = S), 35741-17-4.

(31) Criteria used for establishing identity were superimposable infrared spectra, no depression in mixture melting point, and identical $R_f$ values.

# Synthesis of $\Delta^9$-Isoambrettolide and Its Isomers from 1,9-Cyclohexadecadiene

BRAJA D. MOOKHERJEE,* ROBERT W. TRENKLE, AND RAMAN R. PATEL

*International Flavors & Fragrances, Inc., Research and Development Department, Union Beach, New Jersey 07735*

*Received May 30, 1972*

Monoepoxycyclohexadecene **2** was reduced with lithium aluminum hydride to cyclohexadecenol **3** and then oxidized to the cyclohexadecenone **4**. This was hydroxylated by Brown's oxymercuration–demercuration process to the hydroxy ketones **5a** and **5b** and then acetylated to the corresponding acetoxy lactones **7a–c** which were pyrolyzed to produce $\Delta^9$-isoambrettolide (**8d**) together with small amounts of the mixture of ambrettolide **8a** and its isomers **8b** and **8c**.

Ambrettolide **8a** (lactone of 16-hydroxy-$\Delta^7$-hexadecenoic acid) is the principal odorous constituent of ambrette seed,[1] *Hibiscus Abelmochus*. $\Delta^9$-Isomabrettolide (**8d**), though not a natural product, possesses the characteristic musk note of oil of ambrette seed.[2] Owing to their importance in the perfume industry, several methods[3a–e] have been developed for the synthesis of **8a** and **8d**. In this paper we report a synthesis of $\Delta^9$-isoambrettolide (**8d**) together with small amounts of the mixture of ambrettolide **8a** and its isomers **8b** and **8c** from now available 1,9-cyclohexadecadiene (**1**).[4]

Unsaturated monoepoxide **2**[5] (69%) obtained from **1** was reduced with lithium aluminum hydride to cyclohexadecenol **3** (80%) and then oxidized with Jones reagent to the corresponding ketone **4**[6,7] (80%). Hydration of the isolated carbon–carbon double bond of **4** was achieved by Brown's oxymercuration–demercuration method[8] to produce a mixture of two hydroxy ketones **5a** and **5b** (56%). Though we could not separate **5a** from **5b** by glc methods, the position of the hydroxyl group was determined by the oxidation of the mixture of **5a** and **5b** into the diketones **11a** and **11b**, which were then separated using an analytical glc column (silicone SE-30). The mass spectral fragmentation patterns were used to distinguish between **11a** and **11b**.[7] The mixture of hydroxy ketones **5a** and **5b** thus obtained was then acetylated to the corresponding acetoxy ketones **6a** and **6b** (Scheme I).

Recently we found that macrocyclic ketones could be easily converted to the corresponding lactones in superior yield by treatment with peracetic acid in the presence of boron trifluoride etherate.[9,10] Thus, when cyclododecanone **9a** was treated with 3 mol of peracetic acid at 50° in the presence of boron trifluoride etherate, it was oxidized to cyclododecanolide **10a** in 55% yield. Under similar conditions, cyclohexadecanone **9b** was converted to cyclohexadecanolide **10b** in 46% yield. When the reaction was carried out at 25° for 2 weeks, the yield of **10a** and **10b** was increased to 77 and 54%, respectively. It should be noted that, when boron trifluoride etherate was replaced by either sulfuric acid[10a] or Caro's acid,[10b] the yield of **10b** was 32% (Scheme II).

Therefore, the boron trifluoride etherate method was applied to the acetoxy ketones **6a** and **6b**. Treatment of the mixture of **6a** and **6b** with 4 mol of peracetic acid at 50° in the presence of boron trifluoride etherate afforded acetoxy lactones (42%). This treatment should produce three lactones, *viz.* **7a**, **7b**, and **7c**. All our attempts to separate the individual acetoxy lactones by column chromatography, tlc, and capillary glc methods were unsuccessful. Therefore, the acetoxy lactones mixture was pyrolyzed at 325° under an atmosphere of nitrogen. This produced $\Delta^9$-isombrettolide (**8d**) (80%) together with small amounts (20%) of the mixture of **8a**, **8b**, and **8c**.

## Experimental Section

Melting points were uncorrected. Glc analyses were performed on an F & M 810 instrument using a 5% Carbowax 20M and 5% silicone SE-30 column (0.25 in. × 25 ft). The following spectrometers were used: ir, Beckman IR-5A; nmr, Varian HA-100 ($CCl_4$, TMS as internal standard); mass spectra, CEC Model 21-110 and AEI-MS9 for high resolution spectra. Mass spectral major fragmentation peaks were recorded in decreasing order of intensity except for the molecular ion. Deactivated silicic acid (5%) made by adding 5 ml of water to 95 g of silicic acid (Grace, 100–200 mesh) was used for column chromatography. Sodium sulfate was used for drying purposes.

**8-Cyclohexadecen-1-ol (3).**—To a stirred suspension of lithium aluminum hydride (3.8 g, 0.093 mol) in ether (120 ml) was added slowly a solution of **2**[5] (11.1 g, 0.046 mol) in ether (100 ml) and the mixture was refluxed for 3 hr. The reaction mixture was cooled to 0°, and the excess lithium aluminum hydride was decomposed by the addition of ice–water (100 ml). The ether layer was separated, and the white precipitate was extracted with ether. The combined ether extracts were dried and concentrated to obtain 9.8 g of crude material, which was chromatographed on deactivated silicic acid (100 g); 10–50% ether in hexane eluted **3** (8.75 g, 80%). Glc (Carbowax 20M) showed two peaks due to cis and trans isomers which were isolated by preparative glc: ir (neat, 8-*trans*-cyclohexadecen-1-ol) 3.05, 3.32, 3.42, 3.5, 6.85, 6.95, 7.15, 7.35, 7.43, 7.72, 8.5, 9.1, 9.7, 9.85, 10.0, 10.4, 11.1, 14.0 $\mu$; nmr $\delta$ 1.1–1.7 (m, 22 H, s at 1.3, internal $CH_2$), 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 3.7 (m, 1 H, CHOH), 5.3 (m, 2 H, CH=CH); mass spectrum *m/e* 238 (molecular ion), 80, 41, 55, 67, 81, 220; ir (neat, 8-*cis*-cyclohexadecen-1-ol) 3.05, 3.32, 3.42, 3.50, 6.85, 6.95, 7.15, 7.43, 7.73, 9.10, 9.45, 9.90, 14.0 $\mu$; nmr $\delta$ 1.1–1.7 (m, 22 H, s at 1.32, internal $CH_2$), 2.0 (b, 4 H, $CH_2C{=}CCH_2$), 3.7 (m, 1 H, CHOH), 5.34 (t, 2 H, CH=CH); mass spectrum *m/e* 238 (molecular ion), 80, 55, 41, 220, 67, 81.

*Anal.* Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2290.

(1) M. Kerschbaum, *Ber.*, **60**, 908 (1927).

(2) "The Givaudan Index," Givaudan-Delawana, Inc., New York, N. Y., 1961, p 46.

(3) (a) Haarman and Reimer and M. Kerschbaum, German Patent 449,217, (1926); (b) M. Stoll and R. E. Gardner, *Helv. Chim. Acta*, **17**, 1609 (1934); (c) Baudard, *C. R. Acad. Sci.*, **221**, 205 (1945); (d) S. D. Sabnis, H. H. Mathur, and S. C. Bhattacharyya, *J. Chem. Soc.*, 2477 (1963); (e) H. H. Mathus and S. C. Bhattacharyya, *ibid.*, 3505 (1963).

(4) N. Calderon, E. A. Ofstead, and W. A. Indy, *J. Polym. Sci.*, **5**, 2209 (1967).

(5) B. D. Mookherjee, R. Trenkle, and R. R. Patel, *J. Org. Chem.*, **36**, 3266 (1971).

(6) Ketone **4** could also be made (~50%) either by the direct treatment of epoxide **2** with butyllithium[6] or by the hydroboration–oxidation[7] of **1**.

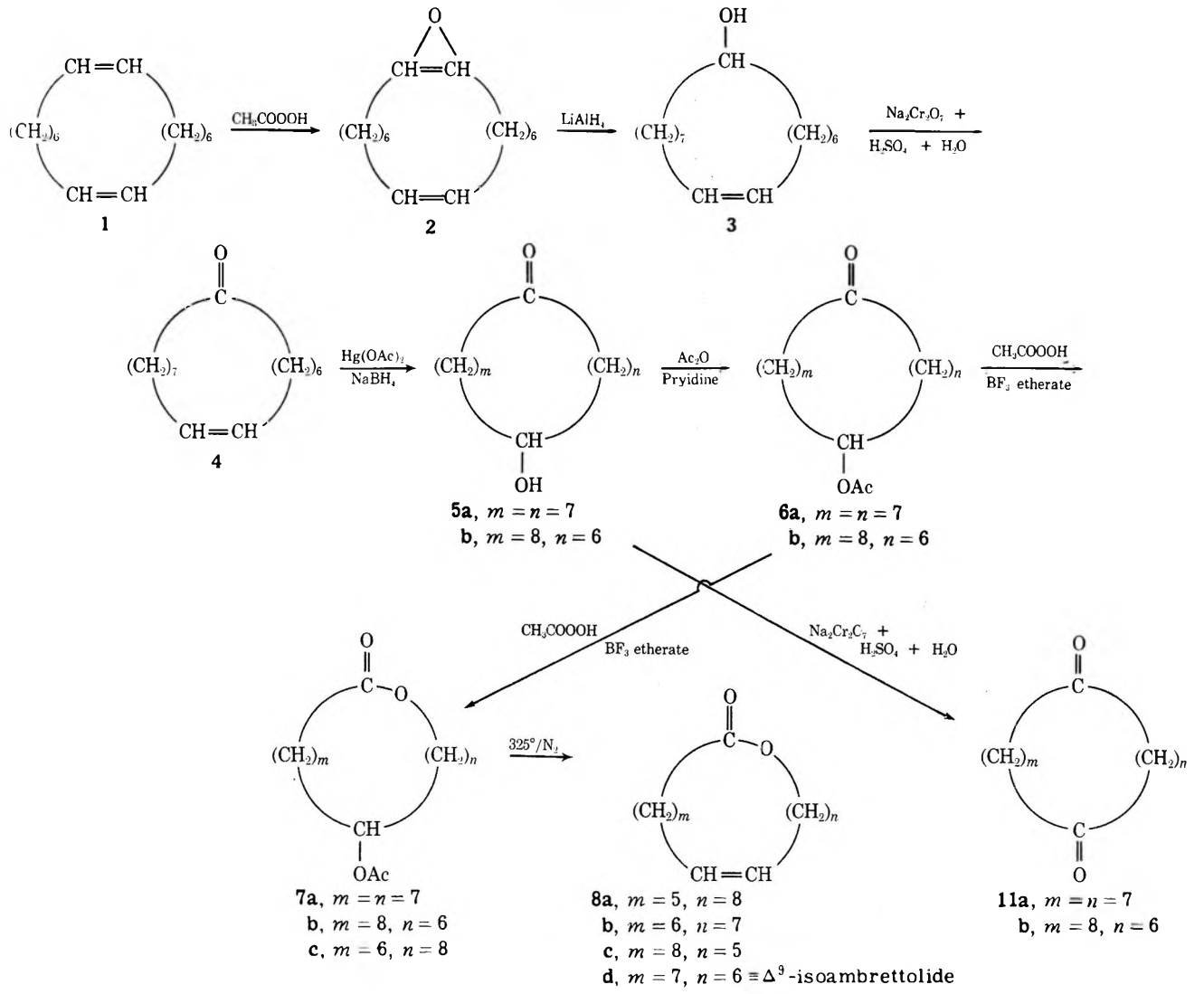
(7) L. Q. Wideman, *J. Org. Chem.*, **33**, 4541 (1968).

(8) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

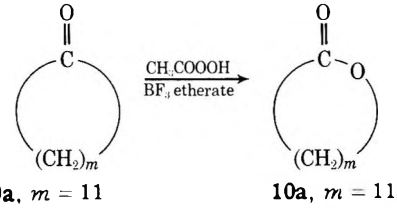
(9) Despite the wide use of boron trifluoride etherate in organic chemistry, its applicability in the Baeyer–Villiger oxidation of macrocyclic ketones to the corresponding lactones with peracetic acid was never explored.

(10) For other known procedures for the conversion of macrocyclic ketones to corresponding lactones, see (a) K. Kosswig, W. Stumf, and Kirchhof, *Justus Liebigs Ann. Chem.*, **681**, 28 (1965); (b) L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

SCHEME I




SCHEME II




**8-Cyclohexadecen-1-one** (4).—A solution of sodium dichromate (6 g) in concentrated sulfuric acid (4.9 ml) and water (25 ml) was added to a stirred solution of **3** (8.7 g, 0.037 mol) in ether (60 ml) over a 0.5-hr period at room temperature, and the mixture was stirred for an additional 3 hr at that temperature. Water (25 ml) was added, and the resulting green mixture was extracted with ether. The ether extract was washed with aqueous sodium bicarbonate solution (5%) and saturated sodium chloride solution, dried, and on evaporation of solvent yielded 8.6 g of crude material which was chromatographed on deactivated silicic acid (90 g); 5–50% ether in hexane (500 ml/fraction) eluted 4[5,6] (6.9 g, 80%). Glc (Carbowax 20M) showed two peaks due to cis and trans isomers: ir (neat, 8-*trans*-cyclohexadecen-1-one) 3.41, 3.5, 5.82 (C=O), 6.82, 6.92, 7.02, 7.09, 7.2, 7.29, 9.0, 9.55, 9.7, 10.3 μ (trans CH=CH); mass spectrum *m/e* 236 (molecular ion), 41, 55, 67, 81; ir (neat, 8-*cis*-cyclohexadecen-1-one) 3.33, 3.41, 3.5, 5.82, 6.81, 6.9, 7.02, 7.09, 7.3, 9.0, 9.8, 10.3 (very weak), 13.95 μ (broad, cis CH=CH–); mass spectrum *m/e* 236 (molecular ion), 41, 55, 67, 81, 29.

*Anal.* Calcd for $C_{16}H_{28}O$: *m/e* 236.2140. Found: *m/e* 236.2148.

**9-Hydroxycyclohexadecan-1-one** (5a) **and 8-Hydroxycyclohexadecan-1-one** (5b).—In a 500-ml flask, fitted with a magnetic stirrer, was placed mercuric acetate (40 g, 0.128 mol). To this was added water (60 ml), followed by tetrahydrofuran (30 ml). An intense yellow color was formed. Then a solution of **4** (16.6 g, 0.065 mol) in tetrahydrofuran (30 ml) was slowly added. The reaction mixture was stirred for 20 hr at room temperature. Then 3 *N* sodium hydroxide (60 ml) was added, followed by a solution of 0.5 *M* sodium borohydride (120 ml) in 3 *N* sodium hydroxide, maintaining the temperature of the reaction mixture at 20° by external cooling. The color of the mixture was changed from yellow to olive. The mercury was allowed to settle. Sodium chloride was added to saturate the water layer and then extracted with ether. The combined ether extracts were washed with sodium chloride solution until neutral, dried, and on removal of solvent yielded 18.8 g of crude material which was chromatographed on deactivated silicic acid (200 g); 10–20% ether in hexane (500 ml/fraction) eluted unreacted **4** (6.5 g) and 50–80% ether in hexane eluted the mixture of **5a** and **5b** (10 g, 56%). Glc (both Carbowax 20M and silicone SE-30) of the mixture of **5a** and **5b** showed one peak: ir (neat) 2.92, 3.4, 3.48, 5.81, 5.88 (weak shoulder), 6.8, 6.84, 6.89, 7.05, 7.25, 7.8, 8.45, 8.6, 8.95, 9.1, 9.75, and 14.0 μ (broad); nmr δ 1.1–1.9 (m, 24 H, with strong s at 1.33, internal $CH_2$), 2.35 (m, 4 H, $CH_2COCH_2$), 3.58 (b, 1 H, CHOH); mass spectrum *m/e* 254 (molecular ion), 55, 41, 43, 57, 69.

*Anal.* Calcd for $C_{16}H_{30}O_2$: *m/e* 254.2245. Found: *m/e* 254.2234.

**9-Acetoxycyclohexadecan-1-one** (6a) **and 8-Acetoxycyclohexadecan-1-one** (6b).—A solution of the mixture of **5a** and **5b** (4

g) in pyridine (12.6 g) and acetic anhydride (6.5 g) was stirred at room temperature for 20 hr. Water (20 ml) was added and extracted with ether. The combined ether extracts were washed successively with dilute (5%) hydrochloric acid, saturated sodium bicarbonate solution, and sodium chloride solution and dried, and on evaporation of solvent yielded the mixture of **6a** and **6b** (4.5 g, 97%). Glc (silicone SE-30) showed two unresolved peaks; ir (neat, mixture of **6a** and **6b**) 3.45, 3.55, 5.79, 5.84, 6.9, 7.1, 6.3, 8.04, 8.95, 9.74, 10.4 $\mu$; nmr $\delta$ 1.1–1.9 (m, 24 H, with strong s at 1.32, internal $CH_2$), 2.0 (s, 3 H, $CH_3COO$–), 2.4 (m, 4 H, $CH_2COCH_2$–), 4.85 (m, 1 H, CHOAc); mass spectrum *m/e* 296 (molecular ion), 43, 55, 41, 236 (M − 60).

*Anal.* Calcd for $C_{18}H_{32}O_3$: *m/e* 296.2351. Found: *m/e* 296.2345.

**Acetoxy Lactones 7 (Probably the Mixture of 7a, 7b, and 7c).**—To a stirred solution of **6a** and **6b** (4.3 g, 0.015 mol) in chloroform (100 ml) was slowly added freshly distilled 98% boron trifluoride etherate (2.1 g, 0.015 mol). Peracetic acid (40%, 12 g, 0.06 mol) was added over a period of 15 min and the reaction mixture was stirred for 12 hr at 50°. The mixture was cooled and water was added. The organic layer was separated, washed with water, dried, and concentrated to obtain 4.2 g of crude material which was chromatographed on deactivated silicic acid (100 g); 10% ether in hexane (500 ml) eluted the mixture of acetoxy lactones **7a–c** (2 g, 44%). Glc (silicone SE-30) showed two unresolved peaks: ir (neat mixture) 3.41, 3.5, 5.75, 6.82, 7.28, 8.02, 8.48, 8.65, 9.0, 9.05, 9.3, 9.5, 9.75, 10.4 $\mu$; nmr $\delta$ 1.1–1.9 (m, 24 H, s at 1.35, internal $CH_2$), 2.0 (s, 3 H, $CH_3COO$), 2.3 (t, 2 H, $CH_2CO$), 4.1 (t, 2 H, $COOCH_2$), 4.85 (m, 1 H, CHOAc); mass spectrum *m/e* 312 (molecular ion), 43, 55, 255, 252, 82.

*Anal.* Calcd for $C_{18}H_{32}O_4$: *m/e* 312.2300. Found: *m/e* 312.2309.

**$\Delta^9$-Isoambrettolide (8d).**—A glass tube (12 × 0.25 in.) filled with nickel turnings was heated to 325° with electrical heating wire. A slow stream of nitrogen (15 ml/min) was passed through the tube, and simultaneously a solution of acetoxy lactones **7** (0.29 g from the previous experiment) in ether (3 ml) was introduced into the tube at a rate of 1 ml/min by means of a 5-ml syringe, followed by 2 ml of ether. The pyrolyzate was collected in two cold traps cooled by a Dry Ice bath. The crude product thus obtained was chromatographed on deactivated silicic acid (10 g); 5–10% ether in hexane (50 ml/fraction) eluted a mixture of products (0.144 g, 62%) whose glc (silicone SE-30) showed one major peak (80%) due to $\Delta^9$-isoambrettolide (**8d**) having a minor shoulder peak (20%) due to the mixture of **8a**, **8b**, and **8c**.

Ir (neat) of $\Delta^9$-isoambrettolide (**8d**): 3.43, 3.51, 5.77, 6.83, 6.93, 7.05, 7.2, 7.4, 8.05, 8.48, 8.74, 8.98, 9.3, 9.45, 9.75, 10.3, 13.85 $\mu$; mass spectrum *m/e* 252 (molecular ion), 82, 41, 67, 96, 55, 81 (all these spectral data are similar to those of authentic *trans*-$\Delta^9$-isoambrettolide from aleuritic acid[3e]).

*Anal.* Calcd for $C_{16}H_{28}O_2$ (**8d**): *m/e* 252.2089. Found: *m/e* 252.2081.

Ir (neat) of the minor peak (mixture of **8a**,[11] **8b**, and **8c**): 3.41, 3.51, 5.75, 6.85, 6.93, 7.05, 7.2, 7.95, 8.49, 9.0, 9.3, 10.10, 10.32, 11.0 $\mu$; mass spectrum *m/e* 252 (molecular ion), 82, 41, 67, 55, 81.

*Anal.* Calcd for $C_{16}H_{28}O_2$: *m/e* 252.2089. Found: *m/e* 252.2094.

**Cyclododecanolide 10a. A. With Boron Trifluoride Etherate at 50°.**—A solution of cyclododecanone **9a** (182.3 g, 1 mol) in chloroform (1 l.) was treated with freshly distilled boron trifluoride etherate (145 g, 1 mol) and 40% peracetic acid (570 g, 3 mol) as in the case of **7**. The usual work-up and distillation gave 108.6 g (54.8%) of **10a**: bp 82–87° (0.5–0.7 mm); ir (neat) 3.45, 3.52, 5.78, 6.9, 7.25, 7.45, 8.0, 8.5, 8.7, 9.1, 9.5, 10.05 $\mu$; nmr $\delta$ 1.1–2.0 (m, 18 H, s at 1.35, internal $CH_2$), 2.35 (diffused t, 2 H, $CH_2COO$), 4.15 (t, 2 H, $COOCH_2$); mass spectrum *m/e* 198 (molecular ion), 41, 55, 29, 27, 42.

*Anal.* Calcd for $C_{12}H_{22}O_2$: *m/e* 198.1619. Found: *m/e* 198.162.

**B. With Boron Trifluoride Etherate at 25°.**—A solution of **9a** (18.2 g, 0.1 mol) in chloroform (100 ml), 40% peracetic acid (57 g, 0.3 mol), and freshly distilled boron trifluoride etherate (2 g) was allowed to react at 25° in the dark for 2 weeks with occasional shaking. The usual work-up and distillation gave 15.8 g (yield 77.2%) of **10a** containing 3% unreacted **9a** (by glc).

**Cyclohexadecanolide 10b. A. With Boron Trifluoride Etherate at 50°.**—A solution of cyclohexadecanone **9b** (2.15 g, 0.009 mol) in chloroform (18 ml) was treated with boron trifluoride etherate (1.3 g, 0.009 mol) and 40% peracetic acid (5.13, 0.027 mol) as in the case of **7**. After usual work-up and chromatography on deactivated silicic acid (75 g) was obtained 1 g (46%) of **10b**: mp 35° (lit.[10b] mp 33–34°); ir (neat) 3.45, 3.51, 5.78, 6.82, 7.2, 7.4, 8.0, 8.5, 8.75, 9.0, 9.35, 9.45, 10.0, 13.9 $\mu$; nmr $\delta$ 1.2–1.8 (broad m, 26 H, s at 1.32, internal $CH_2$), 2.31 (t, 2 H, $CH_2COO$), 4.12 (t, 2 H, $COOCH_2$); mass spectrum *m/e* 254 (molecular ion), 55, 41, 69, 43, 29, 83.

*Anal.* Calcd for $C_{16}H_{30}O_2$: *m/e* 254.2245. Found: *m/e* 254.2250.

**B. With Boron Trifluoride Etherate at 25°.**—A solution of **9b** (1.67 g, 0.007 mol) in chloroform (14 ml), freshly distilled boron trifluoride etherate (0.35 ml), and 40% peracetic acid (5.32 g, 0.028 mol) was kept at 25° in the dark for 2 weeks with occasional shaking. After usual work-up, the crude material was chromatographed on deactivated silicic acid (50 g); 5% ether in hexane (200 ml) eluted 0.96 g (54%) of **10b**.

**C. With Sulfuric Acid and Acetone.**[10a]—To a solution of **9b** (1 g) in glacial acetic acid (7 ml), concentrated sulfuric acid (4 ml) was slowly added at 8–10°. Then a solution of 40% peracetic acid (4.5 g) in acetone (2 ml) was added dropwise, keeping the temperature at 30 ± 2°. The reaction mixture was stirred for 1 hr and worked up to give 0.47 g of material. Glc analysis indicated the presence of 70% of **10b** (yield 30.8%) and 30% of **9b**.

**D. With Caro's Acid.**[10b]—To a stirred solution of **9b** (1 g) in petroleum ether (bp 30–60°) (5 ml) was added dropwise Caro's acid, prepared from concentrated sulfuric acid (40 g), water (7.7 ml), and potassium persulfate (16 g). The resulting dark reaction mixture was stirred for 15 min at 30–40° and then worked up to give 0.35 g (32.8%) of pale yellow oil **10b** which solidified on standing.

**Oxidation of Hydroxy Ketones 5a and 5b.**—A solution of **5a** and **5b** (9.4 g, 0.037 mol) in ether (100 ml) was treated with a solution of sodium dichromater (6.5 g) in concentrated sulfuric acid (6 ml) and water (30 ml) as in the case of **4**. After usual work-up and chromatography on deactivated silicic acid (100 g) was obtained 7.5 g (80%) of diketones **11a** and **11b**.

**Registry No.**—*cis*-**3**, 36504-16-2; *trans*-**3**, 36504-17-3; *cis*-**4**, 5120-20-7; *trans*-**4**, 5365-06-0; **5a**, 34778-01-3; **5b**, 34801-49-5; **6a**, 36547-05-4; **6b**, 36508-26-6; **7a**, 36508-27-7; **7b**, 36508-28-8; **7c**, 36508-29-9; **8a**, 17598-28-6; **8b**, 36508-30-2; **8c**, 36508-31-3; **8d**, 28645-51-4; **10a**, 947-05-7; **10b**, 109-29-5.

**Acknowledgment.**—The authors express their gratitude to Dr. W. I. Taylor. Without his constant encouragement, this paper would probably not have been written. The authors also wish to thank Mr. H. A. Bondarovich for doing all high-resolution mass spectrometric analysis.

(11) Natural ambrettolide **8a** has the following spectral properties: ir (neat) 3.4, 3.5, 5.72, 6.81, 6.9, 7.2, 7.35, 7.74, 7.95, 8.1, 8.4, 8.7, 8.92, 9.2, 9.32, 9.85, 9.95, 10.55, 11.8, 13.4, 13.9 and 14.4 $\mu$ (broad); mass spectrum *m/e* 252 (molecular ion), 82, 41, 55, 67, 96.

# Proton Magnetic Resonance Spectra of Selected 2-Norcarene Derivatives

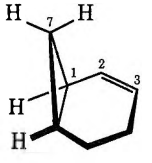
LEO A. PAQUETTE* AND STANLEY E. WILSON[1]

*Department of Chemistry, The Ohio State University, Columbus, Ohio 43210*

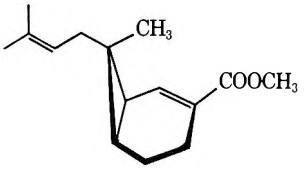
*Received July 5, 1972*

Proton magnetic resonance spectra are given for seven 2-norcarene derivatives. Analyses of these spectra permit one to deduce the syn or anti configuration of a 7-methyl substituent (if present) and the site (C-2 or C-3) of alkyl bonding to the double bond (if relevant). The data given herein should provide useful starting points for configurational and positional assignments to a broad range of 2-norcarene derivatives.

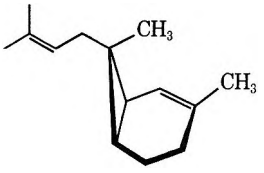
Recently there have been reports from this laboratory describing the isomerization of certain tricyclo[4.1.0.0$^{2,7}$]heptane derivatives to various methyl-substituted 2-norcarenes under conditions of $Ag^+$ catalysis.[2,3] Interest arose immediately in the possibility of making structural assignments to these hydrocarbons by means of pmr methods. In particular, the capability for unambiguous assignment of stereochemistry (syn or anti) at C-7 (see **1**) and for distinction between alkyl substitution at C-2 and C-3 was of principal concern. 2-Carenes and related sesquiterpenoids such as sirenin (**2**)[4] and sesquicarene (**3**)[5] are available from natural souces, but the extent




**1**




**2**

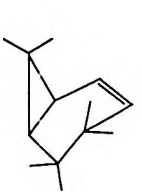



**3**

of substitution in such molecules, particularly at C-7, does not lend itself readily to analysis of simpler systems. Also, although 2-norcarene (**1**) has been known for over a decade,[6,7] no detailed consideration appears to have been given its pmr spectrum. The limited number of known monofunctionalized congeners of **1**[8] have likewise been incompletely studied.

Our interest in the foregoing pmr assignment questions encouraged the preparation of several methylated 2-norcarene derivatives. The selected hydrocarbons which were synthesized attest rather convincingly to the fact that the various isomeric possibilities can be distinguished by pmr spectroscopy.

The 60-MHz pmr spectrum of 2-norcarene (**1**) shown in Figure 1 consists of two low-field multiplets centered approximately at $\delta$ 6.04 and 5.42 which correspond to the nonequivalent pair of olefinic protons, and a series of three high-field multiplets at *ca.* $\delta$ 1.80, 1.23, and 0.68 of relative area 4, 2, and 2, respectively. Of the two conformations available to **1**,[8e,9] pseudo-boat conformation A enjoys a diminished level of non-

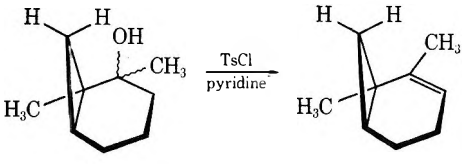


A

B

bonded interaction and allows for greater overlap of of the 1,6 and 1,7 bonds with the p orbital at C-2; consequently, it is favored over the pseudo-chair form (B). In B, the plane of the cyclopropane ring is somewhat tilted away from the double bond, with the result that endo H-7 falls in the shielding cone of the double bond. As will be seen, the adoption by a given 2-norcarene derivative of the pseudo-chair conformation for steric reasons engenders pronounced changes in the chemical shifts of the cyclopropyl and olefinic protons.

The spectrum (Figure 2) of 1,2-dimethyl-2-norcarene (**5**), available by dehydration of alcohol **4** with *p*-




**4** **5**

toluenesulfonyl chloride in pyridine,[3] is somewhat simpler than that of **1**. In this instance, the low-field multiplet must correspond to H-3; this indicates that the H-2 absorption in those 2-norcarenes which adopt conformation A appears downfield from that due to H-3. In general, the $\Delta\delta$ of these absorptions is of the order of 0.3–0.6 ppm.[8a,e] The geminal pair of protons at C-7 appear as a multiplet centered at $\delta$ 0.6; the

(1) National Institutes of Health Postdoctoral Fellow, 1970–1971; National Science Foundation Postdoctoral Fellow, 1971–1972.

(2) L. A. Paquette, R. P. Henzel, and S. E. Wilson, *J. Amer. Chem. Soc.*, **93**, 2335 (1971).

(3) L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *ibid.*, **94**, 7761 (1972).

(4) (a) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *ibid.*, **91**, 4318 (1969); (b) J. J. Plattner, V. T. Bhalerao, and H. Rapoport, *ibid.*, **91**, 4933 (1969); (c) E. J. Corey and K. Achiwa, *Tetrahedron Lett.*, 2245 (1970); (d) V. T. Bhalerao, J. J. Plattner, and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 3429 (1970); (e) J. J. Plattner and H. Rapoport, *ibid.*, **93**, 1758 (1971).

(5) (a) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, 1251 (1968); (b) E. J. Corey and K. Achiwa, *ibid.*, 1837 (1969).

(6) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961).

(7) For more recent syntheses of **1**, consult (a) G. Wittig and F. Wingler, *Chem. Ber.*, **97**, 2146 (1964); (b) C. L. Osborn, T. C. Shields, B. A. Shoulders, J. F. Krause, H. V. Cortez, and P. D. Gardner, *J. Amer. Chem. Soc.*, **87**, 3158 (1965); (c) M. Rey, R. Begrich, W. Kirmse, and A. S. Dreiding, *Helv. Chim. Acta*, **51**, 1002 (1968).

(8) (a) J. J. Sims, *J. Amer. Chem. Soc.*, **87**, 3511 (1965); (b) I. A. D'yakonov, T. V. Domareva-Mandel'shtam, and I. Z. Egenburg, *Zh. Org. Khim.*, **3**, 1441 (1967); *Chem. Abstr.*, **68**, 59166r (1968); (c) B. Besinet, R. Fraisse, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 1377 (1960); (d) D. L. Garin and K. O. Henderson, *Tetrahedron Lett.*, 2009 (1970); (e) W. R. Moore and B. J. King, *J. Org. Chem.*, **36**, 1882 (1971).

(9) S. P. Acharya, *Tetrahedron Lett.*, 4117 (1966).

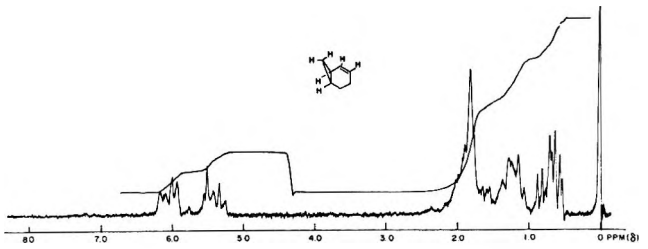


Figure 1.—Pmr spectrum (60 MHz) of 1 in $CDCl_3$ solution.

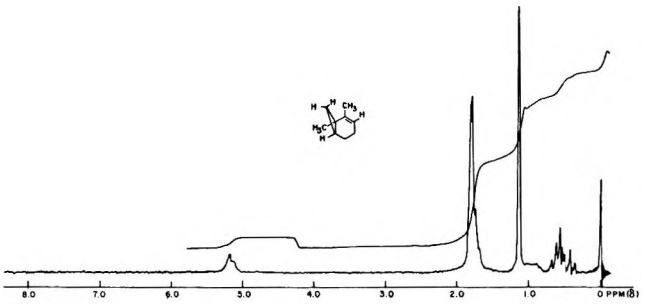
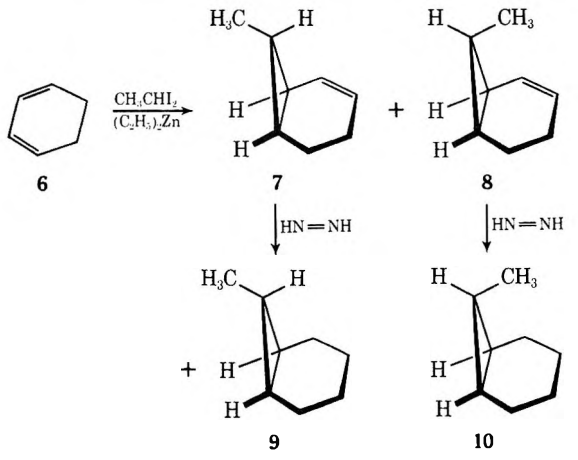


Figure 2.—Pmr spectrum (60 MHz) of 5 in $CDCl_3$ solution.




6 7 8 9 10

remaining cyclopropyl hydrogen (H-6) is seen as a very broad absorption at *ca.* $\delta$ 1.0.

To arrive at the epimeric 7-methyl derivatives **7** and **8**, 1,3-cyclohexadiene (6) was cyclopropanated with 1,1-diiodoethane and diethylzinc according to established procedures.[10] In agreement with earlier observations which denoted preferential formation of the endo epimer under these conditions, **8** dominated the product distribution by a factor of 4.5:1. The isomers were separated by preparative scale gas chromatography and the assigned stereochemistry in each case was established by diimide reduction to the known 7-methylbicyclo[4.1.0]heptanes **9** and **10**.[10,11]

The olefinic hydrogens of exo isomer **7** are again characterized by distinctively different chemical shifts (Figure 3). The magnitude of $\Delta\delta$ in this derivative is approximately 0.7. Introduction of the anti 7-methyl group appears to alter the preferred conformation of the norcarene nucleus only slightly. Though the cyclopropyl protons are somewhat downfield shifted, the

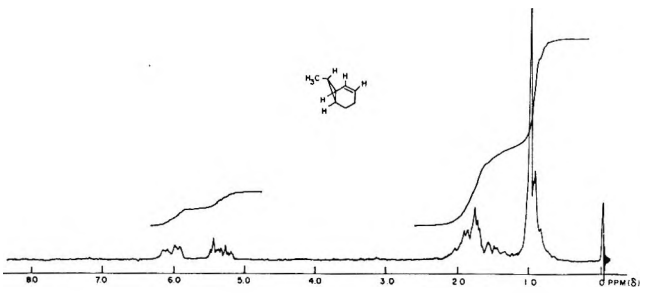


Figure 3.—Pmr spectrum (60 MHz) of 7 in $CDCl_3$ solution.

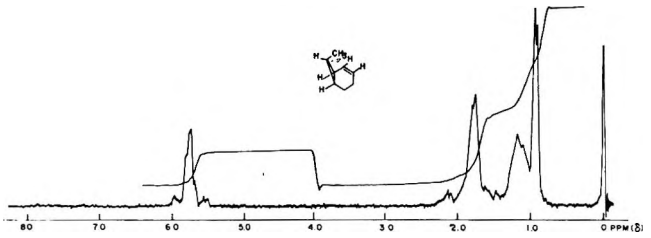


Figure 4.—Pmr spectrum (60 MHz) of 8 in $CDCl_3$ solution.

magnitude of this change may be rationalized in terms of the conventional consequence of alkyl substitution. The effect does not appear to be sufficiently large as to suggest that more substantive conformational alterations have taken place.

In contrast, the olefinic proton absorptions in related endo isomer **8** are seen to have merged into a multiplet of rather narrow width at a field position ($\delta$ 5.78) intermediate between the two extremes present in **7** (Figure 4). Additionally, all three cyclopropyl protons in **8** experience deshielding relative to their counterparts in **7**. In terms of the currently accepted ring current model for cyclopropane, protons in or near the plane of the ring should experience deshielding and those above the ring shielding.[12,13] Additionally, the anisotropic effects of the double bond are such[14] that hydrogen atoms lying in the positive cone are diamagnetically shifted upfield and those lying in the negative cone are shifted downfield. The magnitude of these shifts is recognized to vary with proximity to the symmetrical axis of the $\pi$ bond. An examination of Prentice–Hall molecular models reveals that the steric bulk of the endo 7-methyl group is such as to cause steric compression with the axially disposed C-4 hydrogen in conformer A. To relieve this intramolecular crowding, conformation B is presumably adopted. Accordingly, the varied shielding and deshielding effects of the constituent protons are the consequence of changes in bond and strained ring anisotropies at each of the sites. The observed spectral alterations are of sufficient magnitude to support the concept of conformational crossover.

Scrutiny of the spectrum (Figure 5) of **12**, the 2-norcarene produced exclusively upon treatment of 2-methyl-1,3-cyclohexadiene (**11**) with 1,1-diiodoethane and diethylzinc, likewise revealed the presence of a narrow two-proton olefinic absorption at $\delta$ 5.63. The environment of the $sp^2$ C-bonded hydrogens in **12** must

(10) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3495 (1968); J. Nishimura, N. Kawabata, and J. Furukawa, *Tetrahedron*, **25**, 2647 (1969).

(11) (a) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Amer. Chem. Soc.*, **86**, 1347 (1964); (b) G. Wittig and M. Jautelat, *Justus Liebigs Ann. Chem.*, **702**, 24 (1967); (c) W. L. Dilling and F. Y. Edamura, *Chem. Commun.*, 183 (1967); (d) R. M. Magid and J. G. Welch, *ibid.*, 518 (1967).

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, pp 98–101, and references cited therein.

(13) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 71.

(14) See ref 12, pp 83–88.

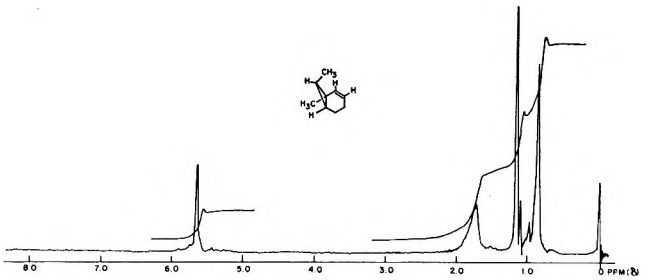


Figure 5.—Pmr spectrum (60 MHz) of **12** in $CDCl_3$ solution.

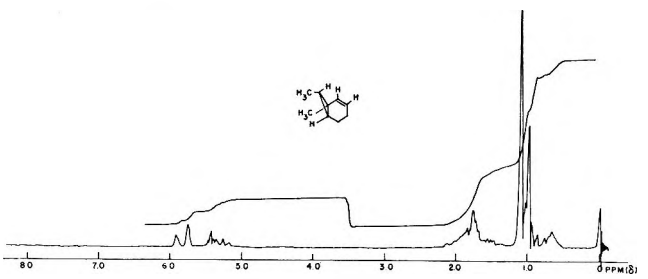


Figure 6.—Pmr spectrum (60 MHz) of **14** in $CDCl_3$ solution.

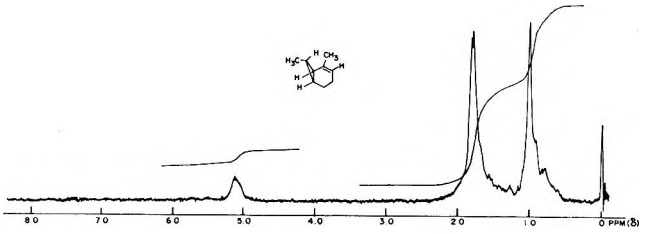
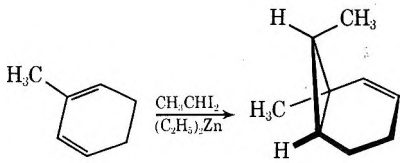


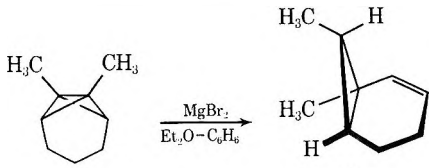
Figure 7.—Pmr spectrum (60 MHz) of **16** in $CDCl_3$ solution.

therefore resemble closely that of the corresponding protons in **8**. It follows that **12** is the endo 7-methyl isomer, an assignment which receives further support at the mechanistic level.[10]



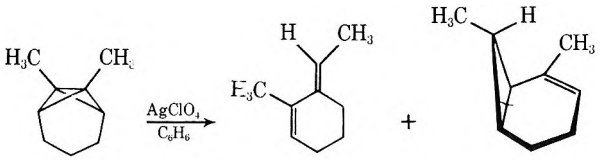
**11** **12**

At this stage it was decided that the stereochemical outcome of the anhydrous magnesium bromide promoted rearrangement of 1,7-dimethyltricyclo[4.1.-$0.0^{2,7}$]heptane (**13**) should be capable of analysis. To this end, a dry benzene solution of **13** was treated with a freshly prepared solution of $MgBr_2$ in anhydrous ether for 2.5 hr at 50°. A single 2-norcarene was obtained, the pmr spectrum of which (Figure 6) clearly differs from that of **12**. In particular, the H-2 and H-3 absorptions are distinctly separated and H-7 now appears at higher field than the methyl peaks. The exo placement of the 7-methyl group is therby revealed. Since the appearance of H-2 as a doublet ($J$ = 10 Hz) requires methyl substitution at C-1, the hydrocarbon produced in this rearrangement (**14**) must be epimeric with **12**. Therefore, the isomerization of tricycloheptane **13** to **14** under these conditions proceeds with retention of configuration at C-7.



**13** **14**

The silver ion catalyzed rearrangement of **13**,[2,3] on the other hand, has been found to give rise to ethylidenecyclohexene (**15**) (80%) and to a 2-norcarene (20%) which proved to be isomeric with **5**, **12**, and **14**, yet distinctly different from these structures.[15] The position of the trigonally bound methyl group can be assigned with certainty at C-2 in view of the absence of the low-field olefinic absorption (Figure 7). Furthermore, because this multiplet appears at $\delta$ 5.00–5.23 and not further downfield, this molecule must reside chiefly in conformation A. Mechanistic reasoning[2,3] places the second methyl group at C-7, and the pmr spectrum indicates that this substituent must be exo oriented as in **16**.



**13** **15** **16**

With these data, chemical shifts and coupling constants necessary for positional and configurational assignment to substituents at positions 1, 2, 3, and 7 in a 2-norcarene are available. We anticipate that these spectral features will prove general in scope and permit structural distinction in a broad range of derivatives.

## Experimental Section[11]

Syntheses of a number of hydrocarbons were achieved according to literature directions. 2-Norcarene (**1**) was prepared by $MgBr_2$-catalyzed isomerization of tricyclo[4.1.0.$0^{2,7}$]heptane,[6] 1,2-dimethyl-2-norcarene (**5**) by dehydration of **4**,[3] and 1,7-dimethyltricyclo[4.1.0.$0^{2,7}$]heptane (**13**) by dimethylation of the parent hydrocarbon.[16] Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer.

*endo*- and *exo*-**7-Methylbicyclo[4.1.0]hept-2-ene (7 and 8).**—The apparatus consisted of a 50-ml flask with reflux condenser, nitrogen inlet, and two pressure-equalizing addition funnels. A diethylzinc cylinder was attached to the top of one addition funnel. The system was evacuated three times by means of a vacuum pump followed by admission of dry nitrogen gas. 1,3-Cyclohexadiene (**6**, 6.0 g, 75 mmol) and diethylzinc (3.7 g, 30 mmol) were introduced into 20 ml of dry pentane, and a solution of 10.30 g (36.5 mmol) of 1,1-diiodoethane in 10 ml of pentane was added dropwise during 1 hr at room temperature. The reaction mixture was allowed to stand overnight and poured into 50 ml of cold dilute hydrochloric acid. When the somewhat vigorous reaction had subsided, 50 ml of pentane was added and the organic phase was washed with saturated aqueous sodium bicarbonate and sodium chloride solutions. The pentane solution was dried and solvent together with unreacted **6** was removed by distillation through a short Vigreux column at atmospheric pressure. The remaining material was distilled at

(15) Masamune and coworkers have erroneously assigned structure **14** to this product: M. Sakai, H. H. Westberg, H. Yamaguchi, and S. Masamune, *J. Amer. Chem. Soc.*, **93**, 4611 (1971).

(16) G. L. Closs and L. E. Closs, *ibid.*, **85**, 2022 (1963).

60° (bath temperature) (10 mm) and the distillate was collected at −78°. Gas chromatographic analysis and separation on a 10 ft × 0.25 in. 5% OV-17 column at 110° showed **7** and **8** to be present in a ratio of 1:4.5. There was collected 90 mg of **7** and 410 mg of **8**.

For **7**: *Anal.* Calcd for $C_8H_{12}$: C, 88.81; H, 11.19. Found: C, 88.52; H, 11.29. For **8**: Found: C, 88.70; H, 11.45.

**Reduction of 7.**—A vigorously stirred solution of 54 mg (0.50 mmol) of **7** and 3.88 g (20 mmol) of dipotassium azodicarboxylate in 6 ml of methanol was treated dropwise during 30 min with 3.0 g (50 mmol) of acetic acid. Stirring was continued until the yellow color had faded, and the reaction mixture was poured onto 25 ml of water and 25 ml of pentane. The water layer was extracted with pentane (10 ml) and the combined organic phases were shaken with saturated sodium bicarbonate solution and dried. The majority of the solvent was removed by careful distillation at atmospheric pressure, and the product (10 mg) was collected on the OV-17 column at 110°. The nmr sample of the hydrocarbon was identical with that of an authentic sample of *exo*-7-methylbicyclo[4.1.0]heptane (**9**).[10,11,17]

**Reduction of 8.**—Like treatment of **8** resulted in the formation of *endo*-7-methylbicyclo[4.1.0]heptane (**10**), whose pmr spectrum was identical in all respects with that of an authentic sample.[17]

***endo*-1,7-Dimethylbicyclo[4.1.0]hept-2-ene (12).**—When a solution of 1.0 g (10.6 mmol) of 2-methyl-1,3-cyclohexadiene (**11**) and 1.6 ml (15 mmol) of diethylzinc in 5 ml of dry pentane was treated dropwise under nitrogen with 5.65 g (20 mmol) of 1,1-diiodoethane dissolved in 3 ml of pentane in the predescribed manner, there was produced a single substance (190 mg isolated after preparative vpc purification on the OV-17 column at 110°) identified as **12**.

*Anal.* Calcd for $C_9H_{14}$: C, 88.45; H, 11.55. Found: C, 88.46; H, 11.55.

**Magnesium Bromide Catalyzed Isomerization of 13.**—To a solution of freshly prepared magnesium bromide in anhydrous ether [2 ml of a solution (bottom layer) prepared from magnesium turnings (excess) and 1,2-dibromoethane (18.8 g, 0.10 mol) in 100 ml of ether] diluted with 6 ml of dry benzene was added 0.44 g (3.6 mmol) of **13**. After 2.5 hr at 50°, the reaction mixture was cooled in ice water and 10 ml of water was cautiously introduced. The organic layer was removed and the aqueous phase was extracted with pentane. The combined organic phases were dried and carefully concentrated at atmospheric pressure. The remaining material was distilled at 60° (bath temperature) (1 mm) and the volatiles were collected at −78°. The lone product was purified by preparative vpc on the OV-17 column at 110° and identified as **14** (21 mg).

*Anal.* Calcd for $C_9H_{14}$: C, 88.45; H, 11.55. Found: C, 88.25; H, 11.71.

**Registry No.**—**1**, 2566-57-6; **5**, 36601-89-5; **7**, 36601-90-8; **8**, 36601-91-9; **12**, 36601-92-0; **14**, 36601-93-1; **16**, 33375-20-1.

**Acknowledgment.**—This work was supported in part with funds provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(17) We thank Professor R. M. Magid for kindly providing us with the requisite pmr spectra.

# Rearrangements Attending Attempts to Form the 1-Dibenzosemibullvalenylcarbinyl (1-Dibenzotricyclo[3.3.0.0$^{2,8}$]octadienylcarbinyl) Cation[1]

STANLEY J. CRISTOL,*[2] GEORGE C. SCHLOEMER,[2] DONALD R. JAMES,[3] AND LEO A. PAQUETTE[3]

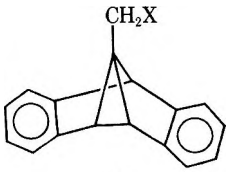
*Departments of Chemistry, University of Colorado, Boulder, Colorado 80302, and The Ohio State University, Columbus, Ohio 43210*

*Received July 25, 1972*

Silver acetate promoted acetolysis of 1-bromomethyl-3,6-dibenzotricyclo[3.3.0.0$^{2,8}$]octadiene (1-Br) and deamination of 1-aminomethyl-3,6-dibenzotricyclo[3.3.0.0$^{2,8}$]octadiene (1-$NH_2$) have been studied. Solvolysis leads only to the rearranged acetates **2**, **3**, **4**, and **5**, along with benzofluorene **6**; "normal" deamination in acetic acid gives, besides **6**, unrearranged acetate 1-OAc and alcohol 1-OH and exo products **2** (acetate and alcohol); and "aprotic" deamination gives **6**, 1-OAc, and 2-OAc. Mechanistic rationalizations of these differing sets of results are offered.

Each of our groups has developed interest in carbonium-ion rearrangements in bridged polycyclic compounds and, in particular, in the question of multiplicity of carbonium-ion intermediates, as well as in the study of dibenzosemibullvalene and its derivatives.[4] These interests overlapped in work on the rearrangements attending treatment of 1-bromomethyl-3,6-dibenzotricyclo[3.3.0.0$^{2,8}$]octadiene (1-bromomethyldibenzosemibullvalene, **1**-Br) with silver acetate in acetic acid (Colorado group) and of the corresponding deamination of **1**-$NH_2$ (Ohio State group). This paper describes the results of those experiments.

When **1**-Br was treated in acetic acid with silver acetate, either at room temperature or at approximately 100°, ready reaction occurred with the formation of four acetate products (2-OAc, **3**-OAc, **4**-OAc, and **5**-OAc) and one hydrocarbon, 3,4-benzofluorene (**6**). Pmr analysis indicated that the reaction mixture comprised 30% 2-OAc, 6% **3**-OAc, 24% **4**-OAc, 23% **5**-OAc, and 16% **6**. No unrearranged **1**-OAc was detectible in the reaction mixture, nor was there any evidence for ring opening to the benzohydryl acetate **7**. That the reaction mixture is the result of kinetic, rather than thermodynamic, control was demonstrated by treatment of a mixture of the four acetates with 0.5 *M* $HClO_4$ in acetic acid at room temperature. The mixture was converted cleanly to **4**-OAc. Treatment with 0.02 *M* $HClO_4$ demonstrated that *endo*-**3**-OAc was more




**1**

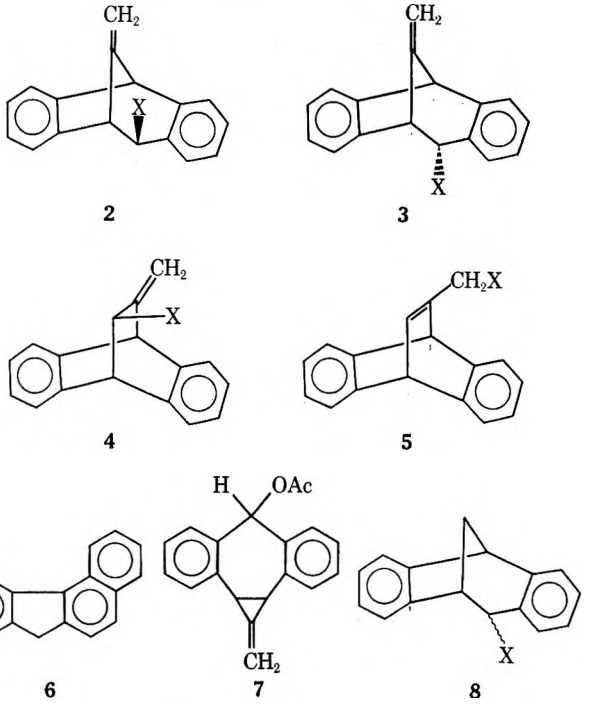
(1) Paper LXXIV in series Bridged Polycyclic Compounds of the University of Colorado group. Paper LXIII: S. J. Cristol, J. R. Mohrig, and G. T. Tiedeman, *J. Org. Chem.*, **37**, 3239 (1972).

(2) University of Colorado. G. C. S. gratefully acknowledges support *via* a NASA fellowship.

(3) The Ohio State University.

(4) See, for example, (a) S. J. Cristol, R. M. Sequeira, and G. O. Mayo, *J. Amer. Chem. Soc.*, **90**, 5564 (1968); (b) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *ibid.*, **92**, 4013 (1970); (c) L. A. Paquette and G. H. Birnberg, *ibid.*, **94**, 164 (1972); (d) L. A. Paquette and G. V. Meehan, *ibid.*, **92**, 3039 (1970).

stable than exo isomer 2, a result consistent with similar properties of the demethylene compounds 8 and



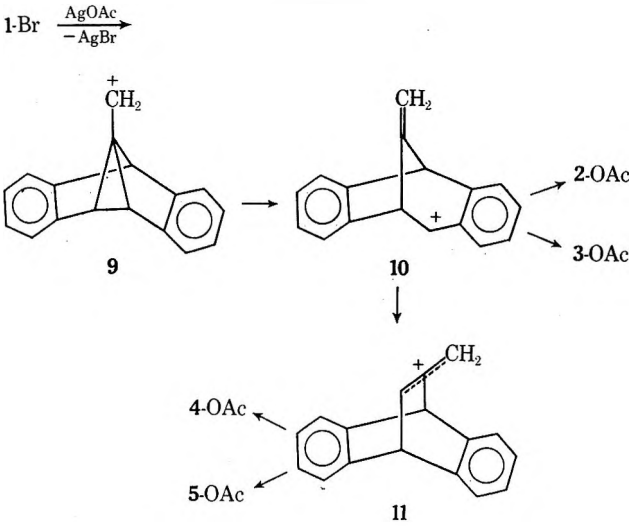
their derivatives.[5] 1-OAc was also readily converted to 4-OAc by acid catalysis.

The product mixture from treatment of 1-$NH_2$ with sodium nitrite in acetic acid was substantially different from that produced by acetolysis of 1-Br. It comprised 16% unrearranged acetate 1-OAc, 12% the corresponding alcohol 1-OH, 24% exo acetate 2-OAc, 40% exo alcohol 2-OH, and 8% 6. None of the endo isomers 3 or of the [2.2.2] products 4 and 5 were found. Deamination of 1-$NH_2$ with isoamyl nitrite in diglyme containing an equivalent of acetic acid led to a mixture containing 33% 1-OAc, 51% 2-OAc, and 16% 6. Again, no endo product 3-OAc or [2.2.2] products 4 and 5 were noted.

The acetate products of the solvolysis experiments with 1-Br can be readily rationalized by the reactions in Scheme I. We have chosen to write classical ion intermediates, rather than nonclassical ones, in these systems for several reasons. First, there is no evidence for the latter, and indeed there is contrary evidence in similar systems where similarly highly stabilized classical ions intervene.[4a,5] Finally, the formation of both exo and endo acetates 2-OAc and 3-OAc can be most readily accommodated to the capture of 10 from either side (with exo capture predominating, as anticipated[5]), although nonclassical intermediates could be devised to accommodate these results. Apparently there is no solvent participation (*i.e.*, direct displacement) in an SN2-like process to give 1-OAc nor is ion 9 captured to give 1-OAc products before rearrangement. Although ion 9 is a cyclopropylcarbinyl cation, it does not appear to be stable enough to resist rearrangement to its allylcarbinyl isomer, the benzylic ion 10, and indeed it seems likely that it is completely by-passed in the reaction process (*e.g.*, 1-Br goes directly to 10; see below).

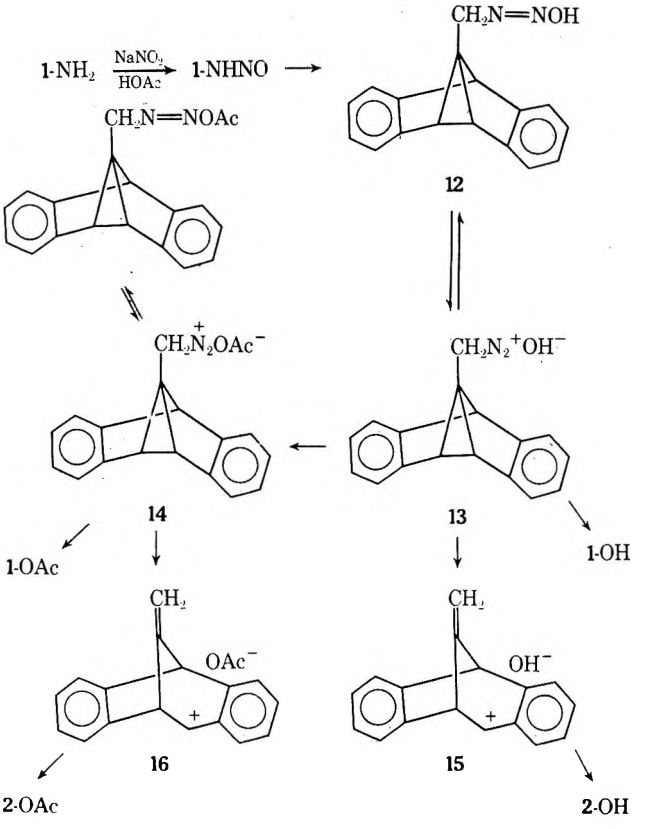
(5) (a) S. J. Cristol and D. D. Tanner, *J. Amer. Chem. Soc.*, **86**, 3122 (1964); (b) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *ibid.*, **87**, 2879 (1965); (c) S. J. Cristol, R. J. Bopp, and A. E. Johnson, *J. Org. Chem.*, **34**, 3574 (1969).

SCHEME I



The deamination results and rationalizations are outlined in Scheme II. Available evidence suggests

SCHEME II



that deamination proceeds through unstable diazohydroxides,[6] which are generally assumed to decay to products, often through ion-pair intermediates. The timing of carbon–nitrogen and nitrogen–oxygen heterolytic bond cleavages is markedly dependent upon structure.[1] When the diazonium ion is long lived, sol-

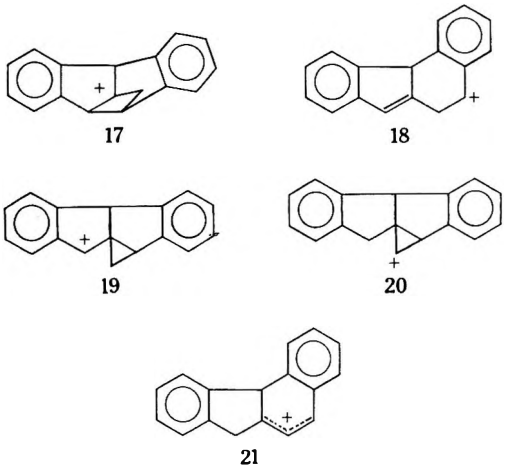
(6) (a) H. Zollinger, "Azo and Diazo Chemistry," Wiley-Interscience, New York, N. Y., 1961, pp 123–136; (b) R. A. M. O'Ferrall, *Advan. Phys. Org. Chem.*, **5**, 362 (1967); (c) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1968, pp 440–483; (d) L. Friedman in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 655–713; (e) C. J. Collins, *Accounts Chem. Res.*, **4**, 315 (1971).

vent exchange occurs, and the product is largely that involving solvent (*e.g.*, acetate ester in acetic acid). On the other hand, it has been proposed[1] that, when the carbonium ion resulting from the loss of nitrogen from the diazonium ion is a very stable one, its formation is either coincident with breaking of the nitrogen–oxygen bond or follows it very shortly, so that there is much capture by the geminate[1] hydroxide ion to give alcohol, often with substantial retention in the alcohol product.[7]

Our results permit us to suggest that the diazonium ion which is produced from 1-$NH_2$ is of medium longevity. We propose that it either reacts with its geminate hydroxide ion to yield the alcohol 1-OH coincident with loss of nitrogen,[8] or that this ion pair exchanges with solvent to give the acetate ion pair **14**. As proposed in Scheme II, either ion pair **13** or **14** can lose nitrogen to give (possibly directly) ion pairs **15** and **16**, respectively. If these ion pairs collapse to products before relaxation (that is, epimeric migration of the counterion), they will yield the exo isomers **2** without the endo isomers. Assuming that isomerization of ion **10** to **11** is slow compared with collapse of **15** and **16**, we can also accommodate the fact that the tight ion pairs **15** and **16** lead by rapid collapse to species **2**, while the solvent-separated ion pairs involved in the solvolysis reactions outlined in Scheme I permit equilibration of **10** and **11** before coordination capture by external solvent species or by counterions.[10]

Thus it seems possible to explain the product differences observed here in the two methods for formation of the carbonium-ion system.

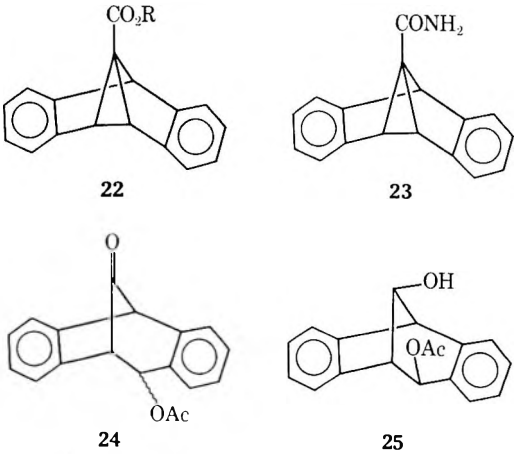
The formation of benzofluorene (**6**) represents a more deep-seated rearrangement than those of the other products. It is of especial interest that **6** is produced only when the carbonium-ion system is entered from 1-X species, and that it is not produced in the solvolyses of 2-Br, 3-Br, 4-Br, or 5-Br, although all of the acetates (except for 1-OAc) are produced in these solvolyses.[11] It therefore must be assumed that the first stage in the formation of **6** is a rearrangement concerted with the loss of nucleofuge[12] and using a path not involving ion **10**. Several pathways appear possible for this rearrangement, assuming classical cations. If the 1,2 (or 1,8) bond migrates, the cyclobutyl cation **17** would form. Cyclobutyl–homoallyl interconversion yields ion **18**, which has the correct carbon skeleton but requires hydride shifts followed by proton loss (or proton loss followed by double-bond isomerization) for aromatization to **6**. Alternatively migration of the 2,8 bond gives the ion **19** which is the cyclopropylcarbinyl isomer of **17**. Also a third alternative involves migration of the benzo ring (a 1,3-aryl migration[4d]) to give **20** followed by cyclopropyl cation to allyl cation rearrangement (it seems likely that these steps would be telescoped) would give **21** which would lose a proton




to give **6**. Each of these proposed routes has at least one less than attractive feature, and we have no labeling experiments to distinguish among the several possibilities, so that these suggestions are speculative, at best.

The reaction of 1-$NH_2$ with isoamyl nitrite in diglyme containing an equivalent of acetic acid deserves further comment. This procedure, which Friedman and Bayless[13] have termed "aprotic diazotization," has been suggested by them to proceed *via* diazo esters produced by addition of acetic acid to the diazoalkanes formed by deprotonation of the diazonium ions in the aprotic solvent system. Our failure to find the alcohols 2-OH or 3-OH in the "aprotic" system would appear to confirm that suggestion, and comparison of results in this system with that in glacial acetic acid, where more than half of the alcohol–acetate fraction is alcohol, provides the beginning of an insight into solvent effects on relative rate constants for the various processes involved.

**Preparation of Reagents and Identification of Products.**—Compounds with the skeleton represented by **1** were derived from 1-carboethoxydibenzotricyclo[3.3.0.$0^{2,8}$]octadiene (22-Et) or its methyl ester analog (22-Me). These compounds are readily available by




(7) (a) R. A. Moss, A. W. Fritz, and E. M. Emery, *J. Org. Chem.*, **36**, 3881 (1971); (b) H. Felkin, *C. R. Acad. Sci.*, **236**, 298 (1953); (c) R. Huisgen and C. Rüchardt, *Justus Liebigs Ann. Chem.*, **601**, 21 (1956).

(8) A number of investigators have suggested direct displacement of nucleophiles upon diazonium ions.[9]

(9) (a) J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, **81**, 4094 (1959); (b) J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 (1964); (c) J. G. Traynham and M. T. Yang, *ibid.*, **87**, 2394 (1965); (d) R. D. Guthrie, *ibid.*, **89**, 6718 (1967); (e) J. H. Bayless, A. T. Jurewicz, and L. Friedman, *ibid.*, **90**, 4466 (1968); (f) W. J. Albery, J. E. C. Hutchins, R. M. Hyde, and R. H. Johnson, *J. Chem. Soc. B*, 219 (1968).

(10) We have looked[11] into the solvolysis of the bromides **2**, **3**, **4**, and **5** (which will be reported later) and have data consistent with the idea that **10** and **11** do equilibrate but that their rates of equilibration are competitive with their rates of capture by solvent.

(11) G. C. Schloemer, Ph.D. Thesis, University of Colorado.

(12) (a) This term for describing a group leaving with an electron pair has been used in Europe for some time.[12b,c] We recommend its further acceptance. (b) J. Mathieu, A. Allais, and J. Valls, *Angew. Chem.*, **72**, 71 (1960); (c) C. A. Grob and P. W. Schiess, *Angew. Chem. Int. Ed. Engl.*, **6**, 1 (1967).

(13) L. Friedman and J. H. Bayless, *J. Amer. Chem. Soc.*, **91**, 1790 (1969).

Ciganek's elegant photochemical procedure.[14] Reduction of **22** with lithium aluminum hydride gave **1-OH**[15] which gave **1-OAc** with acetic anhydride in pyridine. Treatment of **1-OH** with phosphorus tribromide and pyridine in benzene gave **1-Br**.

Treatment of **22-Me** with methanolic sodium hydroxide gave, after acidification, **22-H**, which upon treatment first with thionyl chloride and then with ammonia gave the amide **23**. Diborane reduction of **23** gave **1-$NH_2$**.

The product mixtures from the solvolyses were analyzed by pmr techniques before and after treatment with lithium aluminum hydride to convert the acetates to alcohols, and those from the deamination without lithium aluminum hydride treatment (**4-OH** and **5-OH** are more readily distinguishable than their acetates).

A pure sample of **5-OH** was prepared by lithium aluminum hydride–aluminum chloride reduction[16] of 7-carboethoxydibenzobicyclo[2.2.2]octatriene as described by Shenoy.[17] As reported by Shenoy, omission of aluminum chloride gave the saturated alcohol. **5-OAc** was also prepared from propargyl acetate and anthracene,[15] although the Shenoy procedure for **5-OH** is simpler. Treatment of **5-OAc** (or **2-** or **3-OAc**) with perchloric acid in acetic acid gave **4-OAc**. Pure samples of **2-OAc** or **3-OAc** were not obtained, but mixtures of the two can be readily characterized by the different coupling constants of the carbinyl (C-4) proton with the bridgehead proton.[18] A mixture or **2-OAc** and **3-OAc** was prepared by a Wittig reaction on **24** which was prepared by oxidation of **25**. **25** was prepared by treatment of epoxydibenzobicyclo[2.2.2]octadiene[19] with acetic acid. Compound **6** is known.[20]

## Experimental Section

Pmr spectra were determined on Varian A-60A and HA-100 spectrometers.

**1-Hydroxymethyldibenzotricyclo[3.3.0.$0^{2,8}$]octadiene (1-OH).**[15]—A solution of 3.11 g (11.2 mmol) of 1-carboethoxytricyclo[3.3.0.$0^{2,8}$]octadiene (**22-Et**)[14] and 800 mg of lithium aluminum hydride in 60 ml of tetrahydrofuran was heated at reflux for 24 hr. Work-up in the usual way gave, after treatment with charcoal and recrystallization from petroleum ether (bp 60–70°), 1.60 g (63%) of **1-OH**: mp 147–148° (lit,[4d] mp 146–147°); pmr ($CDCl_3$) $\tau$ 2.5–3.0 (8 H, m, aromatic H), 5.57 (1 H, s, H-5), 6.17 (2 H, s, H-9), 7.01 (2 H, s, H-2, H-8), 8.10 (1 H, s, OH).

**1-Acetoxymethyldibenzotricyclo[3.3.0.$0^{2,8}$]octadiene (1-OAc).**—Treatment of **1-OH** with acetic anhydride in pyridine gave **1-OAc**, mp 144.2–145.5°, after recrystallization from isopropyl alcohol: pmr ($CDCl_3$) $\tau$ 2.6–3.2 (m, 8, aromatic H), 5.56 (s, 3, H-2, H-5, H-8), 6.90 (s, 2, $CH_2O$), 8.08 (s, 3, $CH_3CO$); pmr ($C_6D_6$), the $\tau$ 5.56 singlet divides into $\tau$ 5.68 (s, 1, H-5) and $\tau$ 5.78 (s, 2, H-2, H-8).

*Anal.* Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.80. Found: C, 82.72; H, 5.67.

**1-Bromomethyldibenzotricyclo[3.3.0.$0^{2,8}$]octadiene (1-Br).**—A stirred solution of 250 mg (1.07 mmol) of **1-OH** in 25 ml of reagent grade benzene containing 1 ml of phosphorus tribromide (2.8 g, 10.3 mmol) and 1 ml of pyridine was heated to 60° for 45 min. The reaction mixture was then poured into 50 ml of water and extracted with several 25-ml portions of benzene. The benzene layers were washed with water and sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent and recrystallization (charcoal) from petroleum ether (bp 60–70°) gave 166 mg (52%) of **1-Br**: mp 132.5–135°; pmr ($CDCl_3$) $\tau$ 2.5–3.0 (8 H, aromatic H), 5.51 (1 H, s, H-5), 6.20 (2 H, s, H-9), 6.84 (2 H, s, H-2, H-8).

*Anal.* Calcd for $C_{17}H_{13}Br$: C, 68.70; H, 4.41. Found: C, 69.07; H, 4.52.

**7-Acetoxymethyldibenzobicyclo[2.2.2]octatriene (5-OAc)**, mp 104–105°, was prepared by a diene synthesis between anthracene and propargyl acetate:[15] pmr ($CDCl_3$) $\tau$ 2.0–3.0 (9 H, m, H-8, aromatic H), 5.00 (1 H, s, H-4), 5.10 (1 H, d, H-1, $J$ = 3.3 Hz), 5.33 (2 H, d, H-9, $J$ = 1.3 Hz), 8.19 (3 H, s, acetate). It was converted to **5-OH** by hydrolysis. **7-Hydroxymethyldibenzobicyclo[2.2.2]octatriene (5-OH)** was also prepared by the lithium aluminum hydride–aluminum chloride reduction[16] of 7-carboethoxydibenzobicyclo[2.2.2]octatriene, as described by Shenoy.[17] It melted at 126–127° and had pmr ($CDCl_3$) $\tau$ 2.3–3.0 (8 H, m, aromatic H), 3.35 (1 H, d of d, H-8, $J$ = 1.5, $J$ = 5.0 Hz), 4.98 (1 H, s, H-4), 4.98 (1 H, d, H-1, $J$ = 5.0 Hz), 5.83 (2 H, d, H-9, $J$ = 1.5 Hz), 8.52 (1 H, s, OH).

**4-*exo*-Acetoxy-8-*syn*-hydroxydibenzobicyclo[3.2.1]octadiene (25).**—A solution of 16.2 g (73 mmol) of epoxydibenzobicyclo[2.2.2]octadiene[19] in 200 ml of glacial acetic acid was heated at 50° for 12 hr. Addition of 500 ml of cold water was followed by extraction with several 100-ml portions of ether. The combined ether extracts were washed with water and aqueous sodium bicarbonate and dried ($MgSO_4$). Evaporation of the ether left an oil, which was chromatographed on Merck 71707 alumina and eluted with benzene. The crude **25** weighed 9.2 g (45%) and was recrystallized from benzene: mp 124.5–126°; pmr ($CDCl_3$) $\tau$ 2.5–3.0 (8 H, m, aromatic H), 4.21 (1 H, d, H-4, $J$ = 2.0 Hz), 5.40 (1 H, m, H-8, $J$ = 4.0, $J$ = 4.5, $J$ = 10 Hz), 6.11 (1 H, d, H-1, $J$ = 4.0 Hz), 6.57 (1 H, d of d, H-5, $J$ = 2.0, $J$ = 4.5 Hz), 7.44 (1 H, d, OH, $J$ = 10 Hz), 7.92 (3 H, s, acetate).

*Anal.* Calcd for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.03; H, 5.75.

**4-Acetoxy-8-methylenedibenzobicyclo[3.2.1]octadiene (*exo*-2-OAc, *endo*-3-OAc).**—Solid sodium dichromate (11.5 g, 39 mmol) was added to a stirred solution of 10.0 g (36 mmol) of **25** in 200 ml of glacial acetic acid at room temperature, after which stirring was continued for 45 min. The reaction mixture was poured into water and extracted with ether. The ethereal extracts were washed with water and aqueous sodium bicarbonate and then dried ($MgSO_4$). Evaporation of the solvent left an oil which appeared (pmr) to be mainly **24**. This was not purified but used directly in the Wittig reaction.

A 53% dispersion (446 mg) of sodium hydride (10 mmol) was placed in a flask under a nitrogen atmosphere and washed with pentane several times to remove the mineral oil. The flask was placed in a bath at 75° and 10 ml of dimethyl sulfoxide (DMSO) was added. Reaction proceeded with hydrogen evolution, and, when this stopped, 3.5 g (10 mmol) of methyltriphenylphosphonium bromide[21] dissolved in 30 ml of DMSO was added to the ice-cold solution. After 20 min, 4 g of impure **24** dissolved in 15 ml of DMSO was added. The reaction mixture was stirred overnight. Addition of water was followed by extraction with ether. The ether layer was dried ($MgSO_4$), and evaporation left an oil which upon alumina chromatography and benzene elution gave 400 mg (10%) of a mixture of **2-OAc** and **3-OAc** (~90% **2-OAc**). Although this mixture was not separated, the following pmr absorbances ($CDCl_3$) can be confidently[18] assigned: **2-OAc**, $\tau$ 2.5–3.0 (8 H, m, aromatic H), 4.05 (1 H, d, H-4, $J$ = 2.0 Hz), 4.95 (1 H, s, H-9), 5.03 (1 H, s, H-9), 5.68 (1 H, s, H-1), 6.12 (1 H, d, H-5, $J$ = 2.0 Hz), 7.76 (3 H, s, acetate); **3-OAc**, $\tau$ 2.5–3.0 (8 H, m, aromatic H), 3.75 (1 H, d, H-4, $J$ = 6 Hz), ~4.90 (1 H, s, H-9), ~5.00 (1 H, s, H-9), 6.00 (1 H, d, H-5, $J$ = 6 Hz), 7.76 (3 H, s, acetate). The mixture was reduced with lithium aluminum hydride to give a mixture of **2-OH** and **3-OH**. Pmr data: **2-OH** ($CDCl_3$), $\tau$ 2.5–3.0 (8 H, m, aromatic H), 4.92 (1 H, s, H-9), 4.98 (1 H, s, H-9), 5.25 (1 H, d, H-4, $J$ = 2 Hz), 5.74 (1 H, s, H-1), 6.16 (1 H, d, H-5, $J$ = 2 Hz); **3-OH** ($CCl_4$), $\tau$ 2.5–3.0 (8 H, m, aromatic H), 5.10 (1 H, s, H-9), 5.10 (1 H, d, H-4, $J$ = 5.5 Hz), 5.11 (1 H, s, H-9), 5.80 (1 H, s, H-1), and 6.08 (1 H, d, H-5, $J$ = 5.5 Hz).

**7-Acetoxy-8-methylenedibenzobicyclo[2.2.2]octadiene (4-OAc).**—The acetate mixture from the solvolysis of **1-Br** (4.6 g, 16.6 mmol) (see below) was dissolved in 50 ml of 0.5 *M* perchloric acid in acetic acid. After 40 hr at room temperature, the solution

(14) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 2882 (1966).
(15) This was carried out by Dr. G. O. Mayo, unpublished work.
(16) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1961).
(17) P. K. Shenoy, Ph.D. Thesis, University of Arizona, 1966, p 53.
(18) S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).
(19) S. J. Cristol and R. K. Bly, *J. Amer. Chem. Soc.*, **82**, 6155 (1960).
(20) J. W. Cook, A. Dansi, C. L. Hewett, J. Iball, W. V. Mayneord, and E. Roe, *J. Chem. Soc.*, 1319 (1935).
(21) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954).

was poured into 250 ml of cold water and extracted several times with ether. The ether extracts were combined and washed with water and aqueous sodium bicarbonate. Drying ($MgSO_4$), solvent evaporation, and chromatography on Merck 71707 alumina with benzene elution gave 4.35 g (95%) of 4-OAc, mp 97–98°, after recrystallization from benzene: pmr ($CDCl_3$) $\tau$ 2.5–3.0 (8 H, m, aromatic H), 4.57 (1 H, m, H-7, $J$ = 3.5, $J$ = 1.8, $J$ = 2.0 Hz), 4.78 (1 H, d, H-9, $J$ = 2.0 Hz), 5.07 (1 H, d, H-9, $J$ = 1.8 Hz), 5.31 (1 H, s, H-4), 5.43 (1 H, d, H-1, $J$ = 3.5 Hz), 8.05 (3 H, s, acetate).

*Anal.* Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.80. Found: C, 82.89; H, 6.05.

Lithium aluminum hydride reduction of 4-OAc gave 8-methylene-7-dibenzobicyclo[2.2.2]octadienol (4-OH): mp 148–149° after recrystallization from petroleum ether; bp 60–70°; pmr ($CDCl_3$) $\tau$ 2.5–3.0 (8 H, m, aromatic H), 4.75 (1 H, broad s, H-9), 4.90 (1 H, d, H-9, $J$ = 1 Hz), 5.48 (1 H, s, H-4), 5.62 (2 H, unresolved m, H-1, H-7), 8.20 (1 H, broad s, OH).

*Anal.* Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.29; H, 6.20.

**Silver-Assisted Acetolysis of 1-Br.**—A solution of 100 mg (0.338 mmol) of 1-Br and 100 mg (0.60 mmol) of silver acetate in 30 ml of glacial acetic acid was heated at 90° for 45 min. The cooled solution was filtered and the filtrate diluted with 300 ml of water. Ether extraction, washing with water and aqueous sodium bicarbonate, drying ($MgSO_4$), and solvent evaporation left 95 mg (100%) of an oil which by pmr analysis comprised 30% 2-OAc, 5% 3-OAc, 21% 5-OAc, 24% 4-OAc, and 18% 6. The pmr analysis was done on a solution in deuteriochloroform. Acetate methyl peaks at $\tau$ 8.05 for 4-OAc, 8.00 for 5-OAc, and 7.76 for 2-OAc and 3-OAc gave preliminary data. The C-4 proton absorbances at $\tau$ 4.05 for 2-OAc and at 3.75 for 3-OAc were used to determine the 2:3 ratio. The acetate mixture was reduced to an alcohol mixture with lithium aluminum hydride and the ratio of 5-OH to 4-OH was obtained by integration of the absorbances at $\tau$ 5.22 and 4.7 for 5-CH and $\tau$ 5.83 and 3.41 for 4-OH. Benzofluorene was analyzed by integration of the absorbance at $\tau$ 6.05.

**Separation of Alcohols from Solvolysis Mixtures.**—The acetate mixture from the solvolysis was reduced with lithium aluminum hydride in ether and the oil which resulted was subjected to chromatography on Merck 71707 alumina with elution with 5% ether in benzene. 4-OH, mp 147–148° after recrystallization from petroleum ether, was eluted first, followed by mixtures of 2-OH and 3-OH contaminated by 4-OH. We did not succeed in separating 2-OH and 3-OH. The last fractions contained 5-OH, mp 123–123.5° after recrystallization from petroleum ether.

**Dibenzotricyclo[3.3.0.0$^{2,8}$]octadiene-1-carboxylic Acid (22-H).**—A solution of 2.00 g (7.6 mmol) of 22-Et[14] in 50 ml of 40% aqueous sodium hydroxide and sufficient methanol to cause dissolution was refluxed overnight. The solution was cooled in an ice bath while 20% sulfuric acid was added dropwise with stirring to effect neutralization. The resulting white precipitate was separated by filtration, washed with water, and dried to yield 1.5 g (79%) of the acid. Recrystallization from isopropyl alcohol afforded white needles: mp 229–231°; pmr ($CDCl_3$) $\tau$ −0.57 (s, 1, COOH), 2.5–3.1 (m, 8, aromatic H), 5.03 (s, 1, H-5), 6.14 (s, 2, H-2, H-8).

*Anal.* Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.06; H, 4.88.

**1-Dibenzotricyclo[3.3.0.0$^{2,8}$]octadienecarboxamide (23).**—To a suspension of 5.15 g (20.8 mmol) of 19-H in 60 ml of dry benzene was added 4.84 g (41 mmol) of freshly distilled thionyl chloride and 1.65 g (20 mmol) of dry pyridine. This mixture was refluxed for 1.5 hr. The solvent and excess thionyl chloride were removed *in vacuo* and the residual oil was treated with ~200 ml of ether saturated with ammonia. After standing for 30 min, the ether solution was washed with an equal volume of water and the water layer was reextracted with methylene chloride. The combined organic phases were dried, filtered, and evaporated to give 4.94 g (96%) of **23** as fine white needles: mp 208–209° from hexane–benzene; pmr ($CDCl_3$) $\tau$ 2.5–3.1 (m, 8, aromatic H), 4.29 (br, 2, $NH_2$), 5.25 (s, 1, H-5), 6.25 (s, 2, H-2, H-8).

*Anal.* Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.60; H, 5.18; N, 5.55.

**1-Aminomethyldibenzotricyclo[3.3.0.0$^{2,8}$]octadiene (1-NH$_2$).**—To 40 ml of diborane in tetrahydrofuran (~1 $M$, 40.0 mmol) was added dropwise under nitrogen a solution of 1.66 g (6.73 mmol) of **23** in 60 ml of anhydrous tetrahydrofuran. The solution was refluxed for 8 hr, stirred at room temperature overnight, treated with 6 $N$ hydrochloric acid (~10 ml) until gas evolution was complete, and freed of tetrahydrofuran *in vacuo*. The aqueous emulsion so produced was saturated with sodium hydroxide pellets and extracted with six portions of methylene chloride. The usual work-up furnished 1.41 g (90.4%) of 1-$NH_2$ as a fluffy white powder: mp 180.5–182.5° dec from isopropyl alcohol; pmr ($CDCl_3$) $\tau$ 2.5–3.2 (m, 8, aromatic H), 5.58 (s, 1, H-5), 6.89 (s, 2, H-9), 7.00 (s, 2, H-2, H-8), 8.91 (s, 2, $-NH_2$).

*Anal.* Calcd for $C_{17}H_{15}N$: C, 87.51; H, 6.48. Found: C, 87.74; H, 6.63.

**Protic Deamination of 1-NH$_2$.**—To a solution of 1.5 g (6.44 mmol) of 1-$NH_2$ in 50 ml of glacial acetic acid was added 3.54 g (51.3 mmol) of sodium nitrite in small portions. After the solid dissolved and evolution of nitrogen ceased, the orange solution was poured into a mixture of 75 ml of benzene and 75 ml of water. The water layer was extracted with benzene (8 × 50 ml) and the combined benzene layers were washed with saturated sodium bicarbonate solution (5 × 50 ml), dried, and evaporated. Chromatography on silica served to separate the mixture of acetates from 3,4-benzofluorene (6, 42.2 mg), white plates, mp 124–125° (lit.[4d] mp 125.5–126.5°). The composition of the acetate–alcohol mixture was determined by careful integration of the pmr spectrum. Preparative thick layer chromatographic separation of the mixture led to the isolation of the following components: 2-OAc (171.4 mg), 1-OAc (111.7 mg), 2-OH (239.6 mg), and 1-OH (68.6 mg). The total recovery of products based on starting material was 39%.

**Aprotic Deamination of 1-NH$_2$.**—To a solution of 102 mg (0.44 mmol) of 1-$NH_2$ in 20 ml of anhydrous diglyme (distilled from sodium) was added under nitrogen 26.2 mg (25 μl, 0.44 mmol) of anhydrous acetic acid and 62.8 mg (72 μl, 0.545 mmol) of freshly distilled isoamyl nitrite and the mixture was heated rapidly to 130° by immersing the flask in a preheated oil bath. After 15 min, the orange solution was cooled, poured into 50 ml of water, and extracted with ether (2 × 50 ml). The ether was washed with saturated sodium bicarbonate solution (50 ml) and water (100 ml), dried, and evaporated. Analysis was by pmr. Preparative thin layer chromatography on silica gel (elution with 20% ether in hexane) gave 8.9 mg (15.7%) of 6, 37.1 mg (51.4%) of 2-OAc, and 23.8 mg (32.9%) of 1-OAc. The overall recovery of products was 59%.

**Acid-Catalyzed Rearrangement of 1-OAc.**—1-OAc (50 mg, 0.18 mmol) was dissolved in 10 ml of 0.027 $M$ perchloric acid in acetic acid and this solution was stirred with exclusion of moisture for 9 hr at room temperature. The contents were poured into 10 ml of water and extracted with ether (2 × 25 ml). The customary work-up gave an orange oil, the pmr spectrum of which was superimposable upon that of authentic 4-OAc.

**Registry No.**—1-Br, 28545-62-2; 1-$NH_2$, 34131-53-8; 1-OH, 28545-61-1; 1-OAc, 36481-82-0; 2-OAc, 36357-95-6; 2-OH, 36357-96-7; 3-OH, 36357-97-8; 4-OAc, 36357-98-9; 4-OH, 36357-99-0; 5-OAc, 36358-00-6; 5-OH, 27651-43-9; 22-H, 10589-07-8; 23, 28889-08-9; 25, 36358-02-8.

# Thermodynamics of Formation of the Meisenheimer Complex from Thiophenoxide and 1,3,5-Trinitrobenzene and Heats of Transfer in Methanolic Dimethyl Sulfoxide

JOHN W. LARSEN,* KIRIT AMIN, SHEILA EWING, AND LINDA L. MAGID[1]

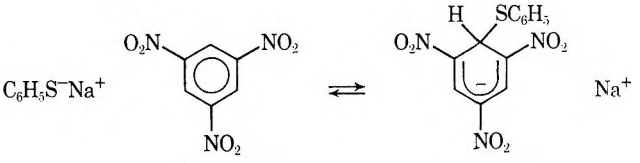
*Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916*

*Received May 15, 1972*

The heat of formation of the Meisenheimer complex formed from sodium thiophenoxide and 1,3,5-trinitrobenzene has been measured in methanol–DMSO mixtures. These data were combined with free energies from the literature to calculate $\Delta S$ for this reaction. Except at very high DMSO concentrations, this reaction is isoentropic across the methanol–DMSO solvent continuum. The heats of transfer of the starting materials and product from methanol to methanol–DMSO mixtures have been measured. The heat of reaction between thiophenoxide and 1,3,5-trinitrobenzene becomes more exothermic as the concentration of DMSO increases. This is due to the fact that the heat of transfer of the Meisenheimer complex from methanol becomes more exothermic as the DMSO concentration increases. The heat of transfer of sodium thiophenoxide also decreases (becomes more exothermic) as the DMSO concentration increases, but it does not change so rapidly as does the heat of transfer of the complex.

Recently the formation of Meisenheimer complexes and related species has been under investigation by a number of groups. The area has been thoroughly reviewed.[2-8] In spite of the intense activity in this area, a good thermodynamic picture has not been developed. Since the complexes are readily prepared and are subject to large solvent effects, an understanding of the solution thermodynamics of these complexes should add significantly to our understanding of solvent effects on complex organic systems. A number of groups have reported equilibrium constants for formation of a variety of Meisenheimer complexes in a number of solvents. However, few enthalpies and entropies of complex formation are available. We have undertaken calorimetric measurements designed to fill this gap.

Since we are interested in solvent effects, we needed a reaction for which both equilibrium constants and heats could be measured in a variety of solvents. Such a reaction is the one between sodium thiophenoxide and 1,3,5-trinitrobenzene (TNB) in methanolic dimethyl sulfoxide.




Crampton[9] has recently published a reliable set of equilibrium constants for this reaction in methanol–DMSO mixtures. We have measured the heat of this reaction calorimetrically and combined these heats of reaction with Crampton's free energies to obtain the entropies of this reaction in a number of methanol–DMSO mixtures. In the course of this work, heats of transfer of the reactants, sodium thiophenoxide and 1,3,5-trinitrobenzene, and a number of related molecules were measured. These data are useful in dissecting the thermodynamics of the complex-forming reaction and also provide a frame of reference for the consideration of solvent effects in this system.

## Experimental Section

The calorimeter[10] and solvent purification[11] have been described previously. Insofar as possible, Crampton's[9] experimental conditions were duplicated. Both thiophenol and 1,3,5-trinitrobenzene were purified commercial samples. Thiophenoxide was prepared in the calorimeter by adding a slight excess of thiophenol to a solution containing sodium methoxide. The heat of solution of the last bit of thiophenol added was always the same as the heat of solution of thiophenol in the solvent being used, indicating that all the methoxide had reacted. All solutions were used immediately after preparation. The heat of reaction between 1,3,5-trinitrobenzene and thiophenoxide was measured at 20 ± 1°.

## Results

The heats of solution of thiophenol, 1,3,5-trinitrobenzene, and methanol in methanol–DMSO mixtures are given in Table I. In all cases, the heats of solution were measured by dissolving at least six 50–100-mg samples of the solute in 200 ml of the appropriate sol-

TABLE I

HEATS OF SOLUTION ($\Delta\bar{H}_S$) OF THIOPHENOL, METHANOL, AND 1,3,5-TRINITROBENZENE (TNB) IN METHANOL–DMSO MIXTURES

| Vol % DMSO in MEOH | $\Delta\bar{H}_{S,C_6H_5SH}$,[a] kcal/mol | $\Delta\bar{H}_{S,TNB}$,[b] kcal/mol | $\Delta H_{S,CH_3OH}$,[b] kcal/mol |
|---|---|---|---|
| 0 | −0.08 ± 0.02 | 3.20 ± 0.34 | 0 |
| 10 | −0.24 ± 0.04 | 2.56 ± 0.14 | 0.02[c] |
| 20 | −0.34 ± 0.07 | 2.38 ± 0.16 | 0.02[c] −0.00 ± 0.02 |
| 30 | −0.39 ± 0.04 | 2.28 ± 0.09 | 0.0[c] |
| 40 | −0.53 ± 0.04 | 2.44 ± 0.26 | −0.01[c] |
| 50 | −0.56 ± 0.03 | 2.25 ± 0.17 | −0.02[c] −0.02 ± 0.04 |
| 60 | −0.62 ± 0.03 | 2.44 ± 0.08 | −0.07[c] |
| 70 | −0.73 ± 0.01 | 2.41 ± 0.02 | −0.12[c] |
| 80 | −0.81 ± 0.04 | 2.48 ± 0.11 | −0.18[c] |
| 90 | | | −0.27[c] −0.25 ± 0.01 |
| 95 | −0.94 ± 0.03 | 2.29 ± 0.22 | −0.30[c] −0.31 ± 0.01 |
| 100 | −0.94 ± 0.12 | 2.45 ± 0.07 | −0.32[c] −0.34 ± 0.01[d] |

[a] At 20 ± 1°. [b] At 25 ± 1°. [c] Data from ref 12. [d] Reference 13, −0.34 kcal/mol.

(1) NSF Predoctoral Fellow, Sept 1969–Aug 1972.
(2) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(3) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).
(4) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev., Chem. Soc.*, **22**, 123 (1968).
(5) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969).
(6) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968.
(7) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969).
(8) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969).
(9) M. R. Crampton, *J. Chem. Soc. B*, 1208 (1968).
(10) E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.*, **35**, 287 (1970).
(11) J. W. Larsen, K. Amin, and J. H. Fendler, *J. Amer. Chem. Soc.*, **93**, 2910 (1971).

vent. The temperature was either 20 ± 1 or 25 ± 1° (see Table I). Since no dependence of the heat of solution on the concentration of the solute was observed, all heats are effectively at infinite dilution. The reported errors are the standard deviation from the average value. Good agreement was found between literature values[12,13] for the heat of solution of methanol in methanolic DMSO and the results reported here.

Table II contains the heats of reaction between 1,3,5-trinitrobenzene and sodium thiophenoxide and also the heats of reaction between thiophenol and sodium methoxide. The reported heats of reaction between thiophenol and sodium methoxide were obtained by measuring the heat of solution of thiophenol in the requisite solvent ($\Delta\bar{H}_S$) and in the same solvent containing an excess of sodium methoxide ($\Delta H_{obsd}$). As shown below, subtraction gives the heat of reaction directly; *i.e.*, $\Delta H_R = \Delta H_{obsd} - \Delta\bar{H}_S$. This technique

TABLE II

HEATS OF REACTION BETWEEN 1,3,5-TRINITROBENZENE AND SODIUM THIOPHENOXIDE AND BETWEEN THIOPHENOL AND SODIUM METHOXIDE AT 20 ± 1°

| Vol % DMSO in MeOH | $\Delta H_{R,TNB+C_6H_5S^-Na^+}$, kcal/mol | $\Delta H_{R,C_6H_5SH+NaOCH_3}$, kcal/mol |
|---|---|---|
| 0 | | −5.15 ± 0.25 |
| 10 | −3.69 ± 0.86[a] | −6.59 ± 0.25 |
| 20 | −4.21 ± 0.10 | −6.74 ± 0.08 |
| 30 | −4.11 ± 0.17 | −7.61 ± 0.26 |
| 40 | −5.11 ± 0.27 | −7.72 ± 0.19 |
| 50 | −5.48 ± 0.07 | |
| 60 | −6.62 ± 0.05 | −8.24 ± 0.29 |
| 70 | −7.10 ± 0.05 | −9.21 ± 0.20 |
| 80 | −7.52 ± 0.15 | −10.17 ± 0.24 |
| 95 | −8.95 ± 0.72 | −11.97 ± 0.09 |
| 100 | −9.93 ± 0.41 | |

[a] Uncertain value. No value was obtained in another attempt in this solvent.

$$NaOCH_{3\,soln} + C_6H_5SH_l \longrightarrow C_6H_5S^-Na_{soln}^+ + CH_3OH_{soln} \quad \Delta H_{obsd}$$

$$C_6H_5SH_l \longrightarrow C_6H_5SH_{so.n} \quad \Delta\bar{H}_S$$

$$NaOCH_{3\,soln} + C_6H_5SH_{soln} \longrightarrow C_6H_5S^-Na_{soln}^+ + CH_3OH_{soln} \quad \Delta H_R$$

was also used for the reaction between 1,3,5-trinitrobenzene and thiophenol when the equilibrium constant was larger than $10^3$. That is, when the equilibrium constant is large and an excess of thiophenoxide is used, essentially all the 1,3,5-trinitrobenzene injected reacts. However, when the equilibrium constant is less than *ca.* $10^3$, the fact that the reaction does not go to completion must be considered. As before,[10] $\Delta H_R = \Delta H_{obsd}/[C]V$, where $\Delta H_{obsd}$ is the observed heat in calories, [C] is the concentration of the complex formed, and $V$ is the volume of the solution. The observed heat, $\Delta H_{obsd}$, is the difference between the heat measured during complex formation and the heat which would have resulted if the 1,3,5-trinitrobenzene had dissolved without reacting. It is the heat due to formation of $[C]V$ moles of complex. The concentration of C formed can be determined easily from the known equilibrium constant $K$ and the concentrations of 1,3,5-trinitrobenzene and sodium thiophenoxide as shown below. The heats of reaction between 1,3,5-trinitrobenzene and thiophenoxide reported here for solutions containing less than 60% (v/v) DMSO are dependent on the values of $K$ used, and are no more accurate than these values. There are two independent checks on the equilibrium constants measured by Crampton[9] that were used here. It is possible to calculate $K$ using enthalpies of reaction measured at different ratios of $[TNB]/[C_6H_5S^-Na^+]$ using a method developed by Bolles and Drago.[14] This method was applied to the calorimetric data and equilibrium constants in agreement with Crampton's were obtained. Feeling that it is better to use independently measured values for $K$ and $\Delta H$ whenever possible, we have utilized Crampton's equilibrium constants throughout. A second less rigorous check is the fact that the $\Delta H$ values which are independent of $K$ form a continuous series with those whose magnitude is dependent on $K$. Reliable data could not be obtained in pure methanol. A number of attempts resulted in calorimetric data which were not consistent with a single equilibrium. The equilibrium constant in this solvent is quite low ($K$ = 1.5) and requires quite precise calorimetric data.[15] It is quite possible that we were unable to obtain the precision necessary to obtain meaningful data. From Crampton's equilibrium constants and the enthalpy values in Table II, $\Delta G$, $\Delta H$, and $\Delta S$ can be calculated for the reaction between sodium thiophenoxide and 1,3,5-trinitrobenzene. These data are contained in Table III.

$$[C] = \{[TNB] + [C_6H_5S^-Na^+] + 1/K \pm \sqrt{([TNB] + [C_6H_5S^-Na^+] + 1/K)^2 - 4[TNB][C_6H_5S^-Na^+]}\}/2$$

TABLE III

THERMODYNAMICS OF THE REACTION BETWEEN 1,3,5-TRINITROBENZENE AND SODIUM THIOPHENOXIDE IN METHANOLIC DMSO AT 20°

| Vol % DMSO in MeOH | $\Delta G$, kcal/mol | $\Delta H$, kcal/mol | $\Delta S$, eu |
|---|---|---|---|
| 0 | −0.37 | | |
| 10 | −0.97 | −3.69 ± 0.86 | −9.29 |
| 20 | −1.42 | −4.21 ± 0.17 | −9.54 |
| 30 | −2.01 | −4.11 ± 0.17 | −7.16 |
| 40 | −2.50 | −5.11 ± 0.27 | −8.90 |
| 50 | −3.05 | −5.48 ± 0.07 | −8.30 |
| 60 | −3.73 | −6.62 ± 0.05 | −9.88 |
| 70 | −4.47 | −7.10 ± 0.05 | −8.98 |
| 80 | −4.92 | −7.52 ± 0.15 | −8.88 |
| 95 | −6.41 | −8.95 ± 0.72 | −8.67 |
| 100 | −6.63 | −9.93 ± 0.41 | −11.27 |

Using the data from Tables I and II together with the heats of solution of sodium methoxide reported in ref 11, it is possible to calculate the heat of transfer of sodium thiophenoxide from methanol to methanol–DMSO mixtures and of the Meisenheimer complex from 10% DMSO (v/v) to solvents richer in DMSO. This

(12) K. Quitzsch, H.-P. Prinz, K. Sühnel, V. S. Pham, and G. Geiseler, *Z. Phys. Chem.*, **241**, 273 (1969).

(13) C. V. Krishnan and H. L. Friedman, *J. Phys. Chem.*, **75**, 3598 (1972).

(14) T. F. Bolles and R. S. Drago, *J. Amer. Chem. Soc.*, **87**, 5015 (1965).

(15) A number of papers have recently appeared on the errors involved in the simultaneous determination of $K$ and $\Delta H$. The precision required can be quite high; see S. Cabani and P. Gianni, *Anal. Chem.*, **44**, 253 (1972), and references cited therein.

is done for sodium thiophenoxide using the enthalpy cycle shown below.

$$\begin{array}{ccc} C_6H_5SH_{S1} + CH_3O^-Na_{S1}^+ & \xrightarrow{\Delta H_{R,1}} & C_6H_5S^-Na_{S1}^+ + CH_3OH_{S1} \\ \downarrow \Delta H_{T,C_6H_5SH} \quad \downarrow \Delta H_{T,CH_3O^-Na^+} & & \downarrow \Delta H_{T,C_6H_5S^-Na^+} \quad \downarrow \Delta H_{T,CH_3OH} \\ C_6H_5SH_{S2} + CH_3O^-Na_{S2}^+ & \xrightarrow{\Delta H_{R,2}} & C_6H_5S^-Na_{S2}^+ + CH_3OH_{S2} \end{array}$$

In the above scheme, solvents 1 and 2 are indicated by subscripts S1 and S2, $\Delta H_R$ is the heat of reaction, and $\Delta H_T$ is a heat of transfer from solvent 1 to solvent 2. Thus $\Delta H_{T,C_6H_5S^-Na^+} = \Delta H_{R_1} + \Delta H_{T,CH_3OH} - \Delta H_{R_2} - \Delta H_{T,CH_3O^-Na^+} - \Delta H_{T,C_6H_5SH}$. A similar cycle can be written for the heat of transfer of the thiophenoxide–1,3,5-trinitrobenzene complex ($\Delta H_{T,comp}$): $\Delta H_{T,comp} = \Delta H_{T,TNB} + \Delta H_{TC_6H_5S^-Na^+} + \Delta H_{R_2} - \Delta H_{R_1}$. These data are shown in Figure 1. Notice that the heats of transfer were measured at 25° while the heats of reaction were measured at 20° to conform to Crampton's data. We feel that the heat capacities are small enough so that heats of transfer at 25° will not be significantly different from heats of transfer measured at 20°.

## Discussion

The thermodynamics of formation of the Meisenheimer complex (Table III) will be considered first. The standard state for the data in Table III is dilute solution in the solvent used. This means that only the difference in $\Delta G$, $\Delta H$, and $\Delta S$ between the starting compounds and the complex in that particular solvent is known. For example, how a change in solvent affects the free energy of the starting materials or product is unknown. However, the effect of a change in solvent on the difference in free energy between the starting materials and product is a known quantity.

The most outstanding feature of the data in Table III is the fact that, except in 100% DMSO, the reaction is isoentropic. Changes in $\Delta H$ are exactly followed by changes in $\Delta G$ while $\Delta S \cong -9$ eu. In the following discussion, the sodium ion will be ignored. No indications of ion pairing were observed; so it seems reasonable that the sodium ion is not taking part in the reaction and its solvation remains the same throughout the reaction. Whenever two molecules combine to form one, there is a large loss of translational entropy. Using the Sakur–Tetrode equation, it can be estimated that the entropy loss occasioned by the formation of this complex in the gas phase is *ca.* −45 eu. To discuss the entropy of Meisenheimer complex formation in solution, the translational entropy loss *in solution* must be known. Unfortunately, it cannot be calculated at present with any accuracy in this system, although attempts in other systems have been made.[16,17] Values of *ca.* −20 have been suggested as reasonable[18] and Jencks has suggested that much lower values (*ca.* −30 to −40 eu) are possible. However, the situation is complicated by the structure of the solvent (unknown) and the interaction of the solvent molecules with the solvent.[17] To the extent that the solute exists in a

(16) M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1678 (1971).
(17) J. W. Larsen, submitted for publication.
(18) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 387.

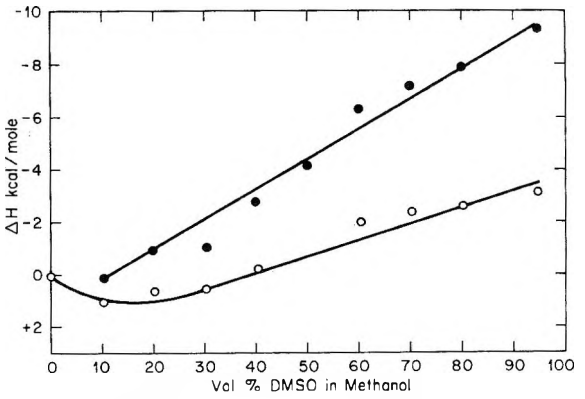
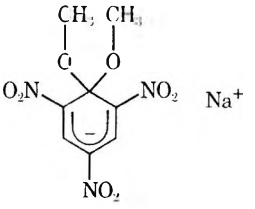



Figure 1.—Heat of transfer of the Meisenheimer complex (●) from 10% DMSO-90% methanol and of sodium thiophenoxide (○) from methanol to methanolic dimethyl sulfoxide at 20°.

"cage" formed by the solvent, the translational motion will be replaced by a vibration within the cage. The loss of these vibrations on combination will not be so large a factor as the loss of translational freedom. If a large negative value for the loss of translational entropy is adopted, then the observed values can be explained as arising from the imposition of a positive entropy term resulting when solvating solvent molecules are freed during the reaction. This means that the resulting Meisenheimer complex does not require so many complexed solvent molecules as do the reactants. Conversely, it can be argued that the observed negative entropy arises from the increased solvation of the complex, compared to the starting materials. It is quite obvious that our knowledge of solvent structure and solvent effects in such systems as this is minuscule and does not allow a decision to be made between the alternative explanations.

The enthalpy of this reaction is somewhat easier to deal with. The heat of transfer of the Meisenheimer complex is nearly identical with that of the related complex 3.[11] Since the two are quite similar in structure,




this is to be expected. It was suggested earlier[11] that this negative heat of transfer arose from stabilization of the highly colored, polarizable complex by DMSO-rich solvents due to London force interactions. Though the heats of transfer for the two complexes are the same, the heat of reaction between thiophenoxide and 1,3,5-trinitrobenzene decreases much less on going from methanol to DMSO than does the heat of reaction between methoxide and 2,4,6-trinitroanisole. The reason for this is obvious from the data in Figure 1. The heat of transfer of sodium thiophenoxide is exothermic, while that for sodium methoxide is quite endothermic.[11] In the reaction involving thiophenoxide, both products and reactants are becoming more stable as the DMSO concentration increases, but the increase in the stabilization of the product is greater.

The thermodynamic data for the reaction between thiophenoxide and 1,3,5-trinitrobenzene can be compared with the few other Meisenheimer complex forming reactions which have been studied in detail. For the reaction of sodium methoxide with 2,4,6-trinitroanisole, $\Delta G$, $\Delta H$, and $\Delta S$ are available from pure methanol to 30% DMSO–methanol (v/v).[19] As mentioned earlier, $\Delta H$ for this reaction decreases quite rapidly, as does $\Delta S$, dropping from +3.05 eu in methanol to −2.45 eu in 30% DMSO–methanol. In general the entropies of reaction of alkoxide ions in alcohols with picrate esters[20] are negative. However, the entropies of their reaction with 1,3,5-trinitrobenzene[20] or cyanonitroanisoles[10] are positive. A thorough study of the reactions of lyate ions in alcohols with 1,3,5-trinitrobenzene exists. Except for hydroxide ion in water (−30.5 eu) and isopropoxide ion in isopropyl alcohol (−9.7 eu), all of the values are between 7.6 and 13.3 eu.[21] Norris has also published a thermodynamic study of the interaction of cyanide ion with 1,3,5-trinitrobenzene in a series of alcohols.[22] Here both $\Delta H$ and $\Delta S$ become more negative as the alcohol becomes less polar. This was interpreted as indicating decreasing solvation of the cyanide ion as the alcohol was varied from methanol to *tert*-butyl alcohol. It seems that specific effects are quite important and there is not yet enough data available to arrive at any general conclusions about solvent effects in these systems.

It is interesting to compare the heats of transfer from methanol to methanol–DMSO for the several compounds for which data are available. The anions will be considered first. In all cases, the cation is sodium and its contribution will be the same in each case; so the observed differences must be due to the anions. For the highly colored, highly polarizable Meisenheimer complexes (sodium salt), the heats of transfer are quite negative (exothermic). For the less polarizable, less delocalized thiophenoxide, the heats of transfer are still negative, but significantly smaller in absolute magnitude than those of the Meisenheimer complexes. For the small, much less polarizable sodium methoxide, the heats of transfer are positive. Thus, as the anion becomes "harder," less polarizable and with a smaller $\pi$ system, it is solvated better by methanol and worse by DMSO. This is as expected.[23] Data are also available for several neutral molecules. The heat of transfer from methanol to 95% DMSO–5% methanol (v/v) of 2,4,6-trinitroanisole and 1,3,5-trinitrobenzene are −1.8 and −0.91 kcal/mol, respectively. The two molecules are similar. Apparently, the loss of hydrogen bonding by the methanol is compensated by the interactions of the $\pi$ system with the dipolar DMSO. The heat of transfer from methanol to DMSO for methanol (−0.34 kcal/mol) and thiophenol (−0.94 kcal/mol) are again consistent with the polarizability of the molecules. However, since these molecules are undoubtedly extensively hydrogen bonded in both solvents, an interpretation in terms of polarizabilities alone is untenable. In Figure 1, the break in the plot of $\Delta H_{trans}$ *vs.* solvent composition for sodium thiophenoxide is unmistakable. Similar breaks are observed for similar plots of the heat of solution of both methanol and DMSO in methanolic DMSO.[12] Such behavior is quite common in aqueous systems and is often interpreted in terms of increased water structure being induced by the organic solute.[24] The reason for this behavior in this system is not clear.

The formation of Meisenheimer complexes is a reaction which is quite easy to study thermodynamically and one which is quite sensitive to solvent changes. As such, it is a good probe of solvent–solute interactions in complex organic systems. Work in this area is continuing.

**Registry No.**—Title Meisenheimer complex, 35886-34-1; sodium thiophenoxide, 930-69-8; 1,3,5-trinitrobenzene, 99-35-4; thiophenol, 108-98-5; methanol, 67-56-1; sodium methoxide, 124-41-4.

**Acknowledgment.**—We are grateful to the Research Corporation for partial support of this work. Support by the National Science Foundation through a predoctoral fellowship (L. L. M.) and undergraduate research support (S. E.) is gratefully acknowledged.

(19) J. H. Fendler and J. W. Larsen, *J. Org. Chem.*, **37**, 2609 (1972).
(20) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 4682 (1970).
(21) L. A. Gan and A. R. Norris, *Can. J. Chem.*, **49**, 2490 (1971).
(22) E. Buncel, A. R. Norris, W. Proudlock, and K. E. Russell, *ibid.*, **47**, 4129 (1969).
(23) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); *Quart. Rev., Chem. Soc.*, **16**, 163 (1962).
(24) F. Franks and D. J. G. Ives, *ibid.*, **20**, 1 (1966).

# Mass Spectral and Thermal Reactions of Dinitrobenzenes

ELLIS K. FIELDS* AND SEYMOUR MEYERSON

*Amoco Chemicals Corporation, Naperville, Illinois 60540, and Standard Oil Company, Naperville, Illinois 60540*

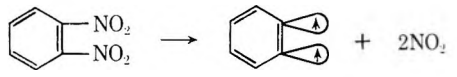
*Received May 9, 1972*

Thermal reactions of dinitrobenzenes can be explained in terms of initial decomposition to $NO_2$ and nitrophenyl radicals, paralleling primary loss of $NO_2$ in the mass spectrum. To some extent the nitrophenyl radicals in turn lose $NO_2$ and give products formally derived from phenylene diradicals. *o*-Dinitrobenzene gives naphthalene derivatives with benzene-$d_6$ and hexafluorobenzene, suggesting some concerted loss of $NO_2$ groups to yield benzyne. Formation of benzofurazan both in the mass spectrum and among thermal reaction products of *o*-dinitrobenzene points to interaction between the nitro groups in this isomer.

Nitrobenzene at 600° decomposes to phenyl radical and $NO_2$.[1] Similar fragmentation of dinitrobenzenes

$$C_6H_5NO_2 \longrightarrow C_6H_5\cdot + NO_2\cdot$$

should give products formally derived from phenylene diradicals. In particular, concerted decomposition of *o*-dinitrobenzene should yield benzyne, perhaps as a diradical, a species for which little evidence thus far has been found in either liquid or gas phase.



In view of the many known parallels between reactions induced by electron impact and thermally, and of the demonstrated usefulness of the former as a guide to the latter,[1] we initiated this work by measuring and studying the mass spectra of the three isomeric dinitrobenzenes. A mass spectrum of only one, the para isomer, has been reported,[2] and our spectrum of this isomer is in good qualitative agreement with the earlier one. Thermal reactions were run at 500–650° with benzene, benzene-$d_6$, and hexafluorobenzene. In addition, the products of reaction of *m*-dinitrobenzene with pyridine, thiophene, and three substituted benzenes at 550° were compared to find any significant variation.

## Experimental Section

The reagents and standards for gas chromatography were purchased from Aldrich and purified, where necessary, by distillation, crystallization, and gas chromatography.

Mass spectra were measured on a modified Consolidated Model 21-103 instrument at 70 eV, with the sample-introduction system and ionization chamber both at 250°. Spectra were measured at the conventional 70 eV and at low voltage, 7.5 eV nominal, except that of the product mixture from reaction of *o*-dinitrobenzene and hexafluorobenzene, which was measured at 9.5 eV to increase sensitivity and thereby facilitate measurement of peak intensities for the large number of low-level components present. For the low-voltage measurements, the repellers were maintained at an average potential of 3 V, the exact values being selected to give maximum sensitivity. Relative intensities in the low-voltage spectra of product mixtures were taken as a first approximation to relative concentrations;[3] in the spectra of labeled materials, they were used for isotopic analysis. Directly coupled gas chromatography–mass spectrometry[4] was used as needed for qualitative identification of products, and gas chromatography, usually on a column of polyethylene glycol sebacate on Chromosorb W, for quantitative analysis.

In a typical experiment, a solution of 16.8 g (0.1 mol) of *m*-dinitrobenzene in 88.88 ml (1 mol) of benzene was pumped into a Vycor tube filled with Vycor chips under nitrogen flowing at 10 cc/min. The tube temperature was 550 ± 4°. Pumping rate was such as to give a contact time in the hot tube of 15 sec. Condensate from the tube was distilled to remove most of the benzene until the pot temperature was 120°; the residue, 25.4 g, was analyzed by gas chromatography with the results shown in Table I.

TABLE I

REACTIONS OF DINITROBENZENES WITH BENZENE[a]

| | Wt %[b] | | |
|---|---|---|---|
| Products | Ortho, 12.5[c] | Meta, 25.4[c] | Para, 12.1[c] |
| Nitrobenzene | 5.9 | 1.0 | 0.4 |
| Phenol | 3.1 | 8.3 | 14.5 |
| Naphthalene | 0.9 | 0.8 | 1.0 |
| Biphenyl | 46.0 | 60.4 | 67.2 |
| Dibenzofuran | 2.5 | 2.3 | 1.6 |
| Dinitrobenzene | 6.6 | 2.3 | 0.5 |
| 2-Nitrobiphenyl | 21.5 | | |
| 3-Nitrobiphenyl | | 1.3 | |
| 4-Nitrobiphenyl | | | 1.7 |
| 2-Hydroxybiphenyl | 2.7 | 0.1 | |
| 3-Hydroxybiphenyl | | 5.2 | |
| 4-Hydroxybiphenyl | 0.7 | 0.5 | 3.2 |
| *o*-Terphenyl | 4.5 | 1.1 | 0.2 |
| *m*-Terphenyl | 1.2 | 10.3 | 1.0 |
| *p*-Terphenyl | 1.1 | 2.3 | 3.4 |
| Unknowns | 3.3 | 4.1 | 5.3 |

[a] Conditions: 0.1 mol of dinitrobenzene, 1 mol of benzene; 550°; contact time, 15 sec; $N_2$, 10 cc/min. [b] Determined by gas chromatygraphy. [c] Total weight of products, grams.

## Results and Discussion

**Mass Spectral Reactions.**—Mass spectra of the dinitrobenzenes are listed in Table II; intensities are expressed in terms of per cent of total ion intensity at masses 26 to 170, inclusive. Partial decomposition schemes deduced from the spectra are shown in Schemes I and II. Wherever a metastable peak was found by us, or is reported elsewhere,[2] to support a postulated decomposition step, a solid arrow is used; otherwise the arrow is broken. The nominal mass and, in parentheses, intensity are shown below each ion formula.

The mass differences characterizing these spectra coincide generally with those found in the spectra of other nitroarenes;[2,5] similar processes are evidently involved. Also paralleling observations on other sets of nitroaromatic isomers are the close similarity of the spectra of *m*- and *p*-dinitrobenzenes and the pronounced differences between them and that of the ortho isomer.[2,5]

(1) (a) E. K. Fields and S. Meyerson, *Accounts Chem. Res.*, **2**, 273 (1969); (b) *Intra-Sci. Chem. Rep.*, **3**, 219 (1969).

(2) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belge*, **29**, 311 (1964).

(3) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **35**, 62 (1970).

(4) R. S. Gohlke, *Anal. Chem.*, **31**, 535 (1959); L. P. Lindeman and J. L. Annis, *ibid.*, **32**, 1742 (1960); J. T. Watson and K. Biemann, *ibid.*, **36**, 1135 (1964).

(5) S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, **88**, 4974 (1966).

TABLE II

MASS SPECTRA OF DINITROBENZENES[a]

| M/z | Ortho | Meta | Para | Metastable transitions | M/z | Ortho | Meta | Para | Metastable transitions |
|---|---|---|---|---|---|---|---|---|---|
| 26 | 0.64 | 0.43 | 0.55 | | 72 | 0.03 | 0.03 | 0.04 | |
| 27 | 0.92 | 0.51 | 0.36 | | 73 | 0.39 | 0.54 | 0.61 | |
| 28 | 0.95 | 0.80 | 0.95 | | 74 | 2.50 | 3.50 | 3.88 | |
| 29 | 0.22 | 0.21 | 0.24 | | 75 | 2.03 | 10.8 | 11.73 | |
| 30 | 26.7 | 17.2 | 21.3 | | 76 | 3.84 | 11.2 | 9.18 | |
| 31 | 0.12 | 0.09 | 0.11 | | 77 | 0.88 | 0.96 | 0.80 | |
| 32 | 0.06 | 0.04 | 0.04 | | 78 | 1.03 | 0.16 | 0.07 | |
| 32.9 (m[b]) | 0.01 | 0.02 | 0.01 | $76^+ \rightarrow 50^+ + 26$ | 79 | 0.13 | 0.12 | 0.05 | |
| 36 | 0.11 | | 0.12 | | 80 | 1.11 | 0.07 | 0.06 | |
| 37 | 1.41 | 1.19 | 1.29 | | 81 | 0.07 | | | |
| 37.5 (d[c]) | 0.01 | 0.01 | 0.01 | | 82 | | | 0.07 | |
| 38 | 2.83 | 1.92 | 2.06 | | 86 | 0.03 | 0.03 | 0.03 | |
| 38.5 (d) | 0.01 | 0.01 | | | 87 | 0.05 | 0.07 | 0.08 | |
| 39 | 5.16 | 1.48 | 1.11 | | 88 | 0.06 | 0.05 | 0.08 | |
| 40 | 0.53 | 0.16 | 0.13 | | 89 | 0.02 | 0.02 | 0.04 | |
| 41 | 0.09 | 0.04 | 0.04 | | 90 | 0.54 | 0.08 | 0.07 | |
| 42 | 0.11 | 0.03 | 0.04 | | 91 | 0.12 | 0.16 | 0.11 | |
| 43 | 0.05 | 0.03 | 0.03 | | 92 | 1.66 | 5.82 | 3.64 | |
| 43.5 (d) | 0.01 | 0.01 | 0.01 | | 93 | 0.19 | 0.45 | 0.29 | |
| 44 | 0.32 | 0.16 | 0.34 | | 94 | 0.72 | 0.04 | 0.03 | |
| 44.5 (m) | 0.003 | 0.01 | 0.01 | $92^+ \rightarrow 64^+ + 28$ | 95 | 0.07 | | | |
| 45 | 0.10 | 0.08 | 0.06 | | 96 | | | 0.02 | |
| 46 | 0.95 | 0.75 | 0.68 | | 103 | 0.03 | | | |
| 48 | 0.05 | 0.05 | 0.05 | | 104 | 0.14 | 0.02 | 0.03 | |
| 49 | 0.52 | 0.49 | 0.48 | | 105 | 0.03 | 0.03 | 0.06 | |
| 50 | 10.0 | 11.4 | 11.3 | | 106 | | 0.08 | 0.18 | |
| 51 | 3.31 | 1.59 | 1.33 | | 107 | | 0.13 | 0.03 | |
| 52 | 1.85 | 0.60 | 0.51 | | 108 | 0.03 | 0.04 | 0.09 | |
| 53 | 2.16 | 0.30 | 0.61 | | 120 | 0.50 | 0.02 | | |
| 54 | 0.16 | 0.16 | 0.22 | | 121 | 0.05 | 0.04 | 0.03 | |
| 55 | 0.05 | 0.19 | 0.03 | | 122 | 0.41 | 4.76 | 4.12 | |
| 56 | | 0.03 | | | 123 | 0.03 | 0.34 | 0.29 | |
| 60 | 0.07 | 0.07 | 0.09 | | 124 | | 0.03 | 0.03 | |
| 61 | 0.39 | 0.47 | 0.56 | | 136 | 0.10 | | | |
| 62 | 0.71 | 0.70 | 0.96 | | 137 | 0.03 | | | |
| 62.0 (m) | 0.09 | 0.03 | 0.04 | $64^+ \rightarrow 63^+ + 1$ | 138 | 0.07 | 0.21 | 0.11 | |
| 63 | 6.94 | 2.65 | 2.72 | | 139 | | 0.02 | | |
| 64 | 6.37 | 3.00 | 3.18 | | 150 | | 0.02 | 0.02 | |
| 65 | 0.48 | 0.30 | 0.29 | | 152 | 0.24 | 0.63 | 0.57 | |
| 66 | 0.34 | 0.15 | 0.11 | | 153 | 0.02 | 0.04 | 0.04 | |
| 67 | 0.18 | 0.05 | 0.04 | | 168 | 6.98 | 11.0 | 10.3 | |
| 68 | 0.24 | 0.03 | 0.07 | | 169 | 0.52 | 0.82 | 0.77 | |
| 69 | 0.03 | | | | 170 | 0.07 | 0.12 | 0.11 | |
| 69.4 (m) | | 0.01 | 0.01 | $122^+ \rightarrow 92^+ + 30$ | | | | | |

[a] Not corrected for naturally occurring heavy isotopes. [b] m denotes a metastable peak. [c] d denotes a peak attributed to a doubly charged ion.

Parent-peak intensity is markedly lower in the spectrum of the ortho isomer than of the others and, together with other differences distributed through the spectra, would seem to reflect the lower thermochemical stability of the ortho isomer.[6] Ions of lower mass in mass spectra are, in general, more likely than heavier ones to arise *via* multistep decomposition processes. Thus, the average masses of all ions in the spectra of related compounds can furnish a crude measure of the relative extents of decomposition. The values derived from the spectra in Table II follow: ortho, 60.5; meta, 75.1; and para, 71.5. Differences in thermochemical stability are evidenced by the heats of combustion[7]—ortho, −703.2; meta, −694.7; para, −692.0 kcal/mol—and by relative decomposition rates as neat liquids at 300°[8]—ortho, 6.8; meta, 1.0; para, 0.38%/hr.

More specifically, several of the strongest peaks in the spectra of the meta and para isomers—at masses 122, 92, 76, and 75—are far less intense in that of the ortho isomer. The differences seem compatible with only two possible explanations. The reaction paths involving the ions of these masses may play a less dominant role in the decomposition of the ortho isomer because of competition with alternative paths, or these ions when formed from the ortho isomer may contain more excess energy, which leads to more extensive decomposition in subsequent reaction steps. That the first of these alternatives is at least a factor is implied by a series of small peaks at masses 136, 120, and 104, corresponding to the loss of two, three, and four oxygen atoms from the molecular ion of the ortho isomer alone. The relative contributions of molecular and atomic

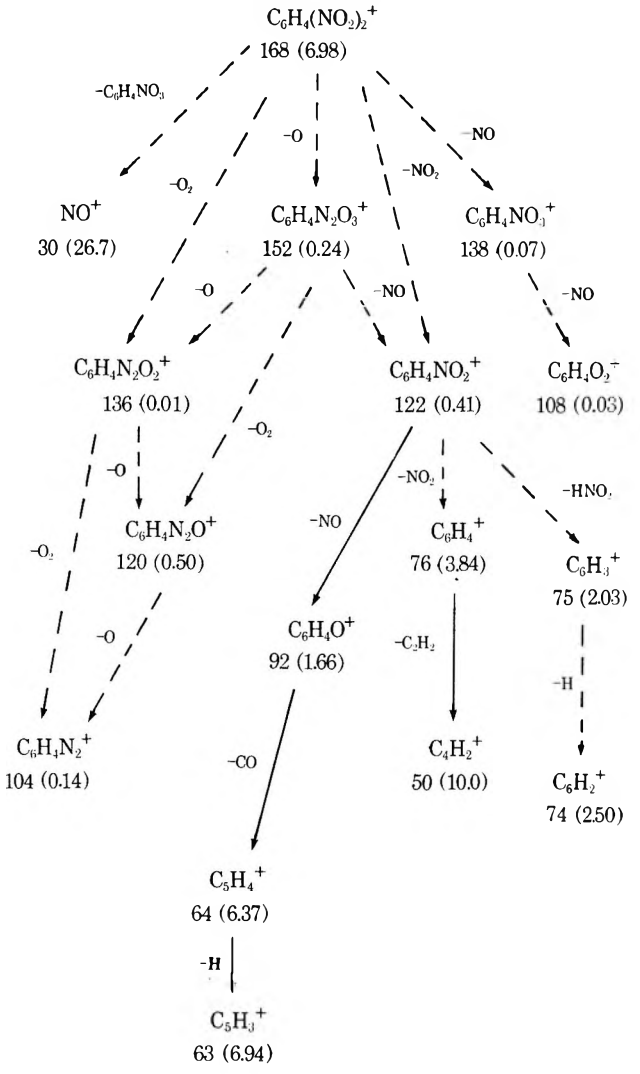
(6) For parallel effects in the mass spectra of stereoisomers, see S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, **1**, 659 (1968); **2**, 603 (1969).

(7) M. S. Kharasch, *J. Res. Nat. Bur. Stand.*, **2**, 359 (1929).

(8) J. C. Hoffsommer, private communication.

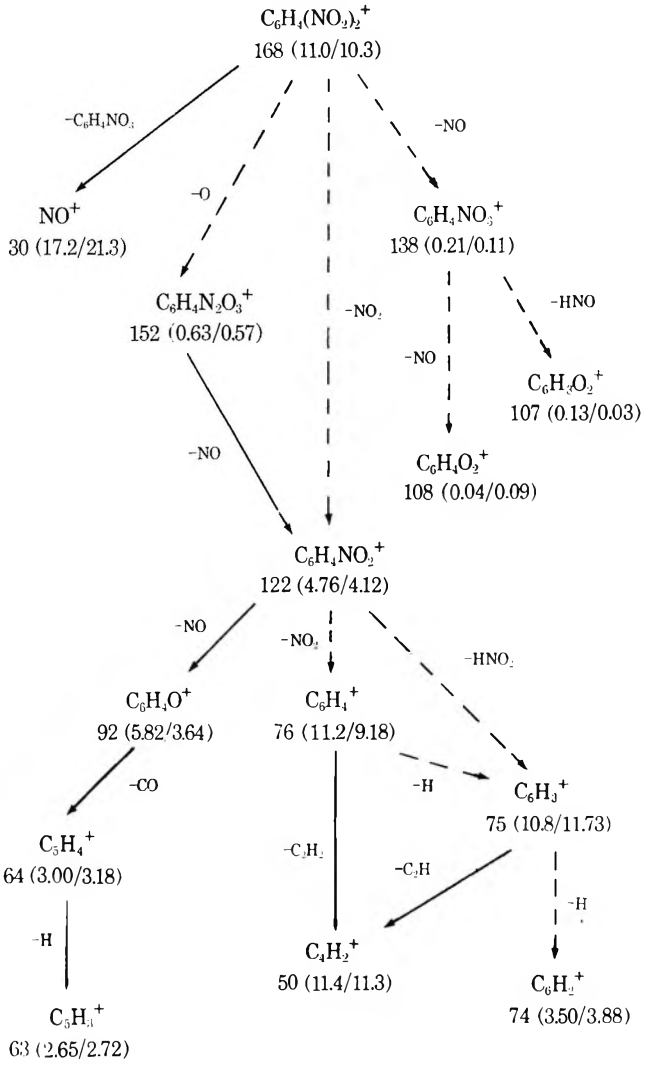
SCHEME I

PARTIAL DECOMPOSITION SCHEME FOR *o*-DINITROBENZENE UNDER ELECTRON IMPACT

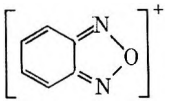



SCHEME II

PARTIAL DECOMPOSITION SCHEME FOR *m*- AND *p*-DINITROBENZENES UNDER ELECTRON IMPACT (META/PARA)




oxygen losses in the formation of these ions are not clear, but interactions of some sort between the neighboring substituents are evidently involved. The products may be stabilized by ring formation, as, for example, for the species of mass 120. Substituted benzo-



mass 120

furazans have been isolated in low yields from thermal reactions of polynitro aromatic compounds.[8-10] Similarly, ions of masses 136 and 120 in the mass spectrum of *o*-nitrophenyl azide have been pictured with the structure of benzofuroxan and benzofurazan, respectively, also paralleling the known thermolysis of *o*-nitrophenyl azide to benzofuroxan.[11]

(9) J. C. Hoffsommer, "Thermal Stability of Polynitropolyphenyl Compounds at Elevated Temperatures," Report NOLTR 67-118, U. S. Naval Ordnance Laboratory, Silver Spring, Md., July 28, 1967.

(10) J. C. Hoffsommer, "Thermal Stability of Polynitroaromatic Amines," Report NOLTR 65-227, U. S. Naval Ordnance Laboratory, Silver Spring, Md., Feb. 16, 1966.

(11) R. A. Abramovitch, E. P. Kyba, and E. F. V. Skriven, *J. Org. Chem.*, **36**, 3796 (1971).

**Thermal Reactions.**—The reaction products of the three dinitrobenzenes with benzene at 550° are shown in Table I. To clarify the origins of these products, we treated the dinitrobenzenes with benzene-$d_6$; to answer some pertinent questions, we used different temperatures for the various isomers. *m*-Dinitrobenzene was allowed to react at 500° to minimize thermal scrambling of protium and deuterium; the isotopic compositions of original and recovered benzenes are identical, showing there was no detectable exchange. A higher temperature seemed desirable for the ortho isomer. A larger amount of the nitrobiphenyl from *o*-dinitrobenzene survived at 550° than from the other two isomers. To induce a possible concerted loss of both nitro groups—or at least in quick enough succession to avoid interruption of the sequence by arylation—we ran its reaction with benzene-$d_6$ at 650°. For comparison, *p*-dinitrobenzene was treated with benzene-$d_6$ under the same conditions as the ortho isomer.

The reactions in Scheme III, with *m*-dinitrobenzene as model, can account for the products listed in Tables I and III. The reaction steps postulated here all have known close analogs in the pyrolysis of nitrobenzene.[1b] The symbol Ph is used to denote a benzene ring or

TABLE III

REACTIONS OF DINITROBENZENES WITH BENZENE-$d_6$[a]

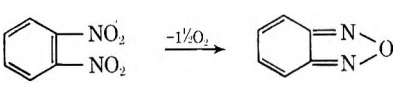
| Product | No. of D atoms | Isotopic distribution, %[b] Ortho, 650° | Meta, 500° | Para, 650° | Summed relative intensity[c] Ortho, 650° | Meta, 500° | Para, 650° |
|---|---|---|---|---|---|---|---|
| Benzene | 0 | 1.0 | | 10.3 | | | |
| | 1 | 0.4 | | | | | |
| | 2 | 0.4 | | | | | |
| | 3 | 0.2 | | | | | |
| | 4 | 1.0 | | | | | |
| | 5 | 8.6 | 3.6 | 8.1 | | | |
| | 6 | 88.4 | 96.4 | 81.6 | 47.0 | 20.3 | 4.4 |
| Phenol | 0 | 25 | 43 | 11 | | | |
| | 1 | 16 | 29 | | | | |
| | 2 | 28 | 28 | 14 | | | |
| | 3 | 19 | | 22 | | | |
| | 4 | 12 | | 36 | | | |
| | 5 | | | 17 | 3.2 | 0.8 | 1.8 |
| Nitrobenzene | 0 | | 14 | | | | |
| | 1 | | 72 | | | | |
| | 2 | | 14 | | | 2.1 | |
| Naphthalene | 4 | 25 | | | | | |
| | 5 | 25 | | | | | |
| | 6 | 12 | | | | | |
| | 7 | 13 | | | | | |
| | 8 | 25 | 100 | 100 | 1.6 | 0.4 | 0.5 |
| Biphenyl | 0 | | 1.8 | | | | |
| | 1 | | | | | | |
| | 2 | | | | | | |
| | 3 | | | | | | |
| | 4 | | | | | | |
| | 5 | 1.9 | | 0.3 | | | |
| | 6 | 8.8 | 0.9 | 1.8 | | | |
| | 7 | 5.1 | 4.5 | 2.7 | | | |
| | 8 | 3.2 | 1.8 | 3.8 | | | |
| | 9 | 12.3 | 0.8 | 4.2 | | | |
| | 10 | 68.7 | 90.2 | 87.2 | 37.4 | 41.0 | 76.9 |
| Dinitrobenzene | 0 | | 100 | | | 1.5 | |
| Hydroxybiphenyl[d] | 2 | | 6 | | | | |
| | 3 | | 10 | 9 | | | |
| | 4 | | 10 | 24 | | | |
| | 5 | 50 | 21 | 47 | | | |
| | 6 | 50 | 53 | 20 | 0.4 | 3.5 | 1.4 |
| Nitrobiphenyl | 4 | | 2 | | | | |
| | 5 | | 85 | | | | |
| | 6 | | 13 | | | 17.7 | |
| Terphenyl | 9 | | | 2 | | | |
| | 10 | 22 | 48 | 10 | | | |
| | 11 | 15 | 24 | 14 | | | |
| | 12 | 15 | 4 | 16 | | | |
| | 13 | 13 | | 18 | | | |
| | 14 | 35 | 24 | 40 | 4.6 | 4.6 | 12.6 |

[a] Conditions: 0.01 mol of dinitrobenzene, 0.1 mol of benzene-$d_6$; isotopic composition of benzene, 3.6% $d_5$; 96.4% $d_6$; contact time, for *m*-dinitrobenzene, 8.5 sec, and, for *o*- and *p*-dinitrobenzenes, 5 sec; $N_2$ at 10 cc/min. [b] Estimated from low-voltage (7.5 ionizing V nominal) mass spectrum. [c] Relative intensity of molecular ions summed for each chemical species in the low-voltage spectrum, normalized to total 100%. Some minor components are omitted from the listing, making the total intensities in the table <100%. [d] Contains some contribution from diphenylamines with one deuterium atom more.

phenyl radical derived solely from benzene, rather than from dinitrobenzene.

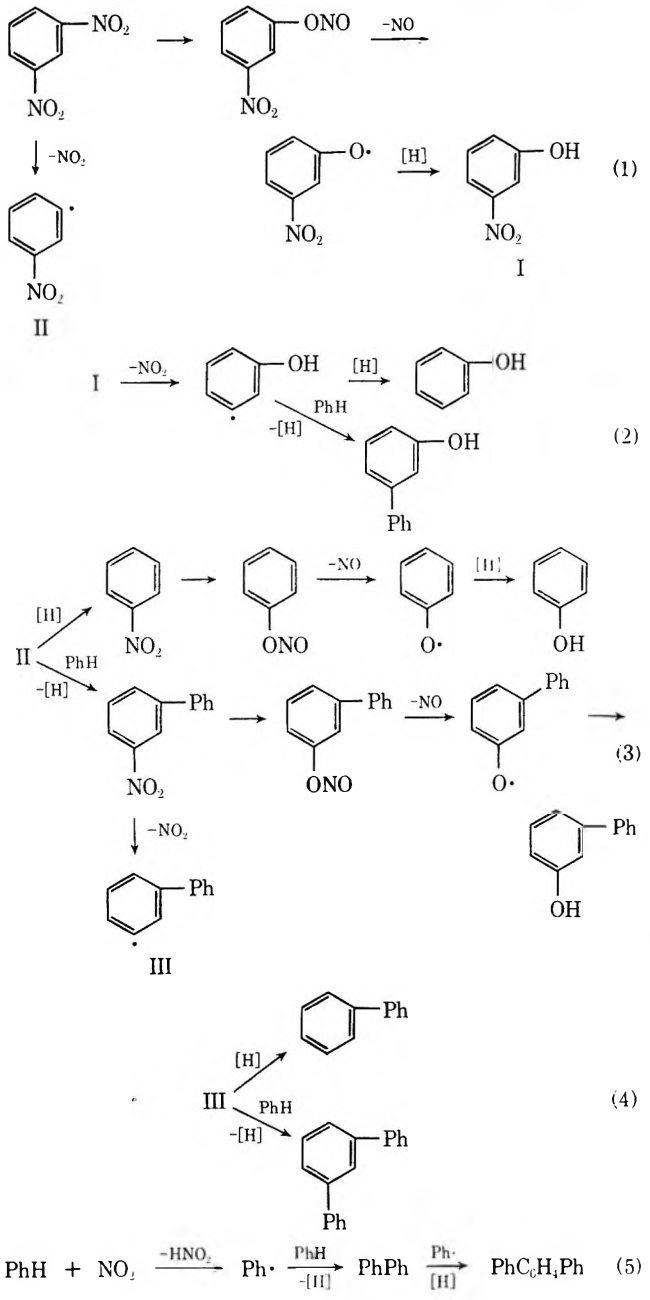
Thermal decomposition of *m*-dinitrobenzene seems to involve a series of consecutive steps that parallel in many ways its decomposition in the mass spectrometer. Loss of $NO_2$ gives nitrophenyl radical (II), which arylates benzene to nitrobiphenyl or abstracts hydrogen to form nitrobenzene. Nitrobiphenyl in turn loses $NO_2$; the biphenylyl radical (III) arylates benzene or abstracts hydrogen to form terphenyl and biphenyl, respectively. The latter reaction is minor, however, for almost all the biphenyl in the labeled run was biphenyl-$d_{10}$, derived solely from the benzene-$d_6$, by reaction 5. About 25% of the terphenyl was formed entirely from benzene-$d_6$, by way of phenyl-$d_5$ radicals from reaction of $NO_2$ with $C_6D_6$ (eq 5).

A minor identified product (0.9% of biphenyl) of mol wt 120 from the thermal reaction of *o*-dinitrobenzene and benzene, but not of the other isomers, proved to be the counterpart of the ion of this mass in the spectrum of *o*-dinitrobenzene by comparison with an authentic



SCHEME III

REACTIONS OF *m*-DINITROBENZENE WITH BENZENE



(1) (2) (3) (4)



(5)

sample. Formation of benzofurazan (2,1,3-benzoxadiazole) seems plausible and, as noted earlier, has precedents in thermal reactions of related materials.

Naphthalene was formed in ~1% yield in the reactions of all three dinitrobenzenes with benzene (Table I). The meta isomer with benzene-$d_6$ (Table III) gave only naphthalene-$d_8$, derived solely from benzene. At 650°, *o*-dinitrobenzene gave naphthalene with four to eight deuterium atoms; the para isomer gave only naphthalene-$d_8$. Total concentrations of naphthalene were, for *p*-dinitrobenzene, about the same as for the meta isomer at 500° and, for *o*-dinitrobenzene, three to four times as much. In spite of the thermal scrambling, the greater amount of naphthalene and its isotopic composition support the formation of benzyne as a minor path in the decomposition of *o*-dinitrobenzene at 650°.

Additional evidence for benzyne from *o*-dinitrobenzene is shown in Table IV, which lists the products

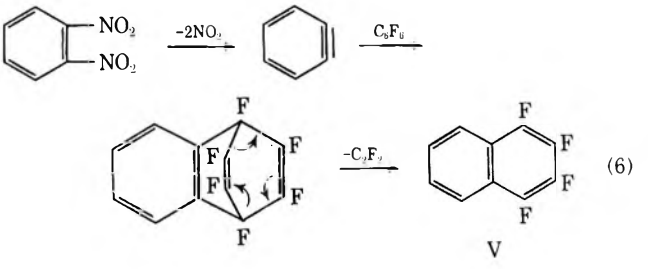
TABLE IV

REACTIONS OF *o*- AND *m*-DINITROBENZENES WITH HEXAFLUOROBENZENE[a]

| Products | Relative concentrations[b] Ortho, 1.05[c] | Meta, 2.35[c] |
|---|---|---|
| Recovered reactants | | |
| Dinitrobenzene | 3.6 | 2.6 |
| Hexafluorobenzene | 33.9 | 9.3 |
| Benzene | 0.3 | 6.7 |
| Pentafluorophenol | 3.3 | 5.2 |
| Tetrafluoronaphthalene | 3.7 | |
| Pentafluorobiphenyl | 1.0 | |
| Hexafluorobiphenyl | 10.2 | 13.0 |
| Heptafluorobiphenyl | | 2.6 |
| Decafluorobiphenyl | 1.1 | 2.6 |
| Decafluoroterphenyl | 0.8 | 29.0 |
| Undecafluoroterphenyl | | 5.2 |
| Other products, mostly unidentified[d] | 42.1 | 23.8 |

[a] Conditions: 0.01 mol of dinitrobenzene, 0.5 mol of hexafluorobenzene; 650°; 10-sec contact time; $N_2$ at 10 cc/min. [b] Per cent of total ions in the low-voltage spectra (9.5 ionizing V nominal for products from the ortho products; 7.5 V from the meta). [c] Total weight of products, grams. [d] In both cases, the spectra gave evidence for a large number of products at low concentrations. Some of the observed peaks may be due to fragment ions arising from low-energy processes.

from the reactions of *o*- and *m*-dinitrobenzenes with hexafluorobenzene under identical conditions. Tetrafluoronaphthalene was formed only from the ortho isomer, presumably by reaction 6.



(6)

The formation of naphthalene derivatives in the reactions of *o*-dinitrobenzene with benzene-$d_6$ and hexafluorobenzene is most readily explained by concerted or fast sequential loss of $2NO_2$ to give benzyne.

To find how the product distributions vary with other substituted benzenes and similar reagents, we allowed *m*-dinitrobenzene to react with fluoro- and chlorobenzenes, benzonitrile, pyridine, and thiophene. The products are listed in Table V.

Reactions of *m*- and *p*-dinitrobenzenes, as well as most reactions of *o*-dinitrobenzene, can be explained in terms of initial decomposition to $NO_2$ and nitrophenyl radical, paralleling primary loss of $NO_2$ in the mass spectra. To some extent, the nitrophenyl radical in turn loses $NO_2$ and gives products formally derived from phenylene diradical, although the actual intermediacy of such a diradical remains in doubt. The identification of benzofurazan both in the mass spectrum and among thermal reaction products of *o*-dinitrobenzene points to an alternative and unexpected interaction between the nitro groups in this isomer.

TABLE V

REACTIONS OF *m*-DINITROBENZENE[a]

| Products | Relative concentrations[b] | | | | |
|---|---|---|---|---|---|
| | Fluorobenzene (R = $C_6H_4F$), 2.2[c] | Chlorobenzene (R = $C_6H_4Cl$), 2.75[c] | Benzonitrile (R = $C_6H_4CN$), 2.5[c] | Pyridine (R = $C_5H_4N$), 2.3[c] | Thiophene (R = $C_4H_3S$), 1.15[c] |
| Phenol | 8 | | | 5 | 9 |
| ROH | 13 | 6 | 18 | 13 | |
| $RC_6H_5$ | 46 | 26 | 99 | 36 | 116 |
| $RC_6H_4OH$ | 11 | | 13 | 15 | 67 |
| RR | 100 | 100 | 100 | 100 | 100 |
| $RC_6H_4NO_2$ | 9 | 24 | 10 | 11 | 22 |
| $RC_6H_4R$ | 21 | 13 | 36 | 37 | 110 |

[a] Conditions: 0.01 mol of *m*-dinitrobenzene, 0.1 mol of reagent; 550°; 15-sec contact time; $N_2$ at 10 cc/min. [b] Relative intensities in the low-voltage mass spectrum normalized to RR = 100. [c] Total weight of products, grams.

**Registry No.**—*o*-Dinitrobenzene, 528-29-0; *m*-dinitrobenzene, 99-65-0; *p*-dinitrobenzene, 100-25-4; benzene, 71-43-2; hexafluorobenzene, 392-56-3.

**Acknowledgment.**—We are grateful to D. K. Albert of the American Oil Co. for his assistance with gas chromatographic analyses, to F. E. Saalfeld of the Naval Research Laboratory, Washington, D. C., and J. C. Hoffsommer of the Naval Ordnance Laboratory, Silver Spring, Md., for helpful suggestions, and to Dr. Hoffsommer for unpublished results and for guidance to relevant research reports. In addition, we thank Harry Heaney of the University of Technology, Loughborough, for an authentic sample of 1,2,3,4-tetrafluoronaphthalene.

# Ring Strain Effects. V.[1] An Electron Spin Resonance Study of the Anion Radicals of a Series of O-Disubstituted Benzenes

STEPHEN E. BALES[2] AND REUBEN D. RIEKE*

*Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514*

*Received May 26, 1972*

The effects of ring strain on spin densities of aromatic radical anions has been investigated for a series of substituted benzene derivatives. The spin density was found to increase at the positions $\alpha$ to the ring juncture carbons containing the fused strained ring. The results are described in terms of a hybridization–polarization mechanism. Also, ion-pairing effects on spin densities are discussed.

The effects of a strained fused ring on the chemical and physical properties of aromatic hydrocarbons has been the subject of much research. Numerous reports have appeared concerning the increased preference for electrophilic attack $\beta$ to the fused ring as strain is increased.[3-9] Markgraf has reported on the changes in the basicity of the lone pair of electrons of a nitrogen $\alpha$ to a fused ring.[10] Also, it has been reported that the acidity of protons $\alpha$ to the fused ring increases as the ring strain is increased.[11,12] An orbital hybridization–polarization model has been put forth which is in accord with these observations.[11,12] Several different types of physical and chemical properties have been interpreted within this model: nmr data,[13,14] epr data,[1,15] rates of protodesilylation,[16] polarographic reduction potentials,[17] molecular orbital calculations,[18] and ir data.[19]

In this paper, we would like to report the epr spectra of a series of benzene derivatives with varying amounts of strain in the fused rings. The results are discussed in terms of the hybridization–polarization model. Effects of ion-pairing on spin densities are also examined. The compounds examined and the numbering system used are shown in Chart I. Hyperfine splitting constants (hfsc) are given in gauss throughout the text.

## Experimental Section

The general techniques and procedures employed for preparing the radical anions in this study have been discussed previously.[15d]

(1) For paper IV in this series, see R. D. Rieke, S. E. Bales, C. F. Meares, and L. Rieke, *J. Amer. Chem. Soc.*, submitted for publication.

(2) NDEA Fellow, 1967–1970; Ethyl Fellow, 1970–1971.

(3) J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, **21**, 1665 (1965).

(4) J. B. F. Lloyd and P. A. Ongley, *ibid.*, **20**, 2185 (1964).

(5) G. Berthier and A. Pullman, *Bull. Soc. Chim. Fr.*, 88 (1960).

(6) H. Tanida and R. Muneyuki, *Tetrahedron Lett.*, 2787 (1964).

(7) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **21**, 245 (1965).

(8) A. R. Bassindale, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc. B*, 12 (1969).

(9) R. Taylor, *J. Chem. Soc. B*, 536 (1971); R. Taylor, *ibid.*, 1559 (1968); J. Blatchly and R. Taylor, *ibid.*, 1402 (1968); R. Taylor, G. Wright, and A. Homes, *ibid.* 780 (1967).

(10) J. H. Markgraf and W. L. Scott, *Chem. Commun.*, 296 (1967); J. H. Markgraf and R. J. Katt, *Tetrahedron Lett.*, 6067 (1968); J. H. Markgraf and R. J. Katt, *J. Org. Chem.*, **37**, 717 (1972).

(11) R. A. Finnegan, *ibid.*, **30**, 1333 (1965).

(12) A. Streitwieser, Jr., G. Ziegler, P. Mowery, A. Lewis, and R. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

(13) G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20**, 1179 (1964).

(14) J. H. Markgraf, R. J. Katt, W. L. Scott, and R. N. Shefrin, *J. Org. Chem.*, **34**, 4131 (1969).

(15) (a) R. D. Rieke, C. F. Meares, and L. I. Rieke *Tetrahedron Lett.*, 5275 (1968); (b) R. D. Rieke, S. E. Bales, P. M. Hudnall, and C. F. Meares, *J. Amer. Chem. Soc.*, **92**, 1418 (1970); (c) R. D. Rieke and W. E. Rich, *ibid.*, **92**, 7349 (1970); (d) R. D. Rieke, S. E. Bales, P. M. Hudnall, and C. F. Meares *ibid.*, **93**, 697 (1971); (e) R. D. Rieke and S. E. Bales, *Chem. Phys. Lett.*, **12**, 631 (1972).

(16) A. R. Bassindale, C. Earborn, and D. R. M. Walton, *J. Chem. Soc. B*, 12 (1969).

(17) R. D. Rieke W. E. Rich, and T. H. Ridgway, *Tetrahedron Lett.*, 4381 (1969); R. D. Rieke, W. E. Rich, and T. H. Ridgway, *J. Amer. Chem. Soc.*, **93**, 1962 (1971).

(18) R. D. Rieke *J. Org. Chem.*, **36**, 227 (1971).

(19) R. D. Rieke and W. E. Rich, unpublished work.

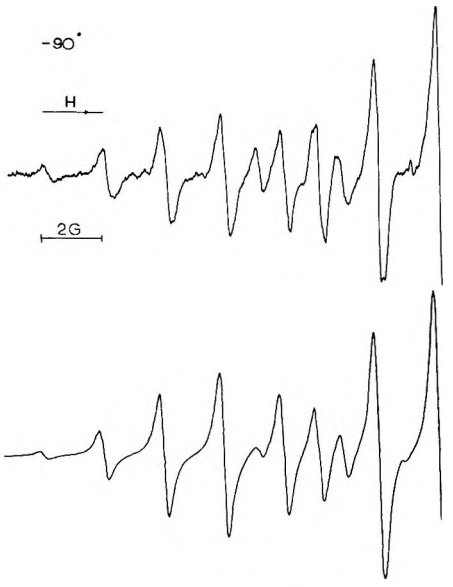
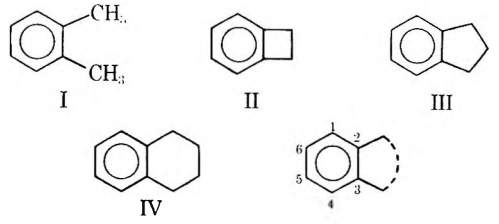



Figure 1.—Esr spectrum of the radical anion of I: upper, experimental spectrum at −90°; lower, calculated −90° spectrum using a line width of 0.25 G.

CHART I

*o*-DISUBSTITUTED BENZENES INVESTIGATED IN THIS STUDY AND THE NUMBERING SYSTEM USED




Epr spectra were recorded on a Varian E-3 spectrometer with X-band frequencies and an E-3 variable temperature accessory.

*o*-**Xylene** (I), **indan** (III), **and tetralin** (IV) were obtained from Aldrich and were purified by gc prior to use.

**Benzocyclobutene** (II, BCB) was prepared by the procedure of Cava and Napier;[20] it was purified by gc and had the same boiling point and spectral characteristics as those reported.

## Results

**Preliminary Studies.**—Meares[21] observed metal splittings when compounds I–IV were reduced using potassium and dimethoxyethane (DME). In an attempt to prepare the free or solvent-separated ion pairs, the compounds were reduced using various volume ratios of DME and hexamethylphosphoramide (HMPA), and the initial hydrocarbon concentration was varied. Since several members of this series had reduced with some difficulty and showed weak signals in potassium and DME,[21] it was decided to begin the study using an initial hydrocarbon concentration of 1 *M*. This was done for III, but the spectra indicated that the concentration could be lowered; so no other compounds were investigated under these conditions.

**Reduction with Potassium in DME (90%) and HMPA (10%). Initial Hydrocarbon Concentration 0.1 *M*.**[22]—Reduction of I gave a dark blue solution and reversible spectra from −60 to −90° which exhibited very little temperature dependency. The signal decayed rapidly above −55°. At −90° the spectra could be simulated quite well using the following hfsc: $A_{1,4}$ = 7.00, $A_{CH_3}$ = 2.00, $A_{5,6}$ = 1.95. Potassium splittings were not observed. The experimental and simulated spectra are shown in Figure 1. These values are close to those reported by Bolton[23] for the reduction of *o*-xylene in potassium and DME at −80°: $A_{1,4}$ = 6.93, $A_{CH_3}$ = 2.00, $A_{5,6}$ = 1.81, $A_K$ = 0.17.

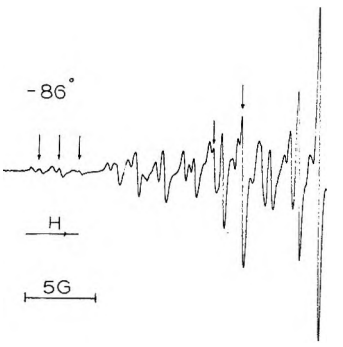



Figure 2.—Esr spectrum of the radical anion of II. The arrows indicate lines due to the free ion.

Compound II was reduced to give a dark green solution and reversible spectra from −5 to −86°. Both the free ion and the ion pair were observed,[15d] the amount of free ion being favored by lowering the temperature. However, the ion pair is the dominant species over the temperature range studied. The spectra at −86° is shown in Figure 2, the arrows indicating some of the lines due to the free ion. The same effects were observed as were seen when BCB was reduced using potassium and DME.[15d] However, potassium splittings were not observed. At −80° the ion pair had hfsc of $A_{1,4}$ = 7.68, $A_{CH_{2\alpha}}$ = 5.70, $A_{CH_{2\beta}}$ = 5.30, and $A_{5,6}$ = 1.45, while the free ion exhibited hfsc of $A_{1,4}$ = 7.45, $A_{CH_2}$ = 5.40, and $A_{5,6}$ = 1.45. At −70°, the free ion was no longer detected. Table I shows the hfsc observed for the ion pair from −70 to −5°. Comparison of these values to those obtained in potassium and DME[15d] shows that here the $A_{1,4}$ value is slightly larger than the value at the corresponding temperature in potassium and DME. Also, the methylenes coalesce at a lower temperature in this solvent system.

TABLE I

HFSC OBSERVED FOR THE ION-PAIRED RADICAL ANION OF II

| *T*, °C | $A_{1,4}$ | $A_{CH_{2\alpha}}$ | $A_{CH_{2\beta}}$ | $A_{5,6}$ |
|---|---|---|---|---|
| −70 | 7.63 | 5.70 | 5.20 | 1.45 |
| −60 | 7.60 | 5.68 | 5.20 | 1.45 |
| −50 | 7.50 | 5.55 | | 1.45 |
| −35 | 7.50 | 5.44 | | 1.40 |
| −20 | 7.46 | 5.40 | | 1.40 |
| −5 | 7.40 | 5.37 | | 1.40 |

Reduction of III gave a dark green solution which turned yellow-orange upon warming. Reversible spectra were obtained from −50° to −90° and showed little temperature dependency. The spectra were simulated using hfsc of $A_{1,4}$ = 7.50, $A_{CH_{2\alpha}}$ = 3.75 (4 H), $A_{CH_{2\beta}}$ = 0.80, and $A_{5,6}$ = 1.50. Experimental and simulated spectra for −90° are shown in Figure 3.

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

(21) C. F. Meares, B. S. Honor Thesis, University of North Carolina, Chapel Hill, N. C., 1968.

(22) The percentages represent a volume composition.

(23) J. R. Bolton, *J. Chem. Phys.*, **41**, 2455 (1964).

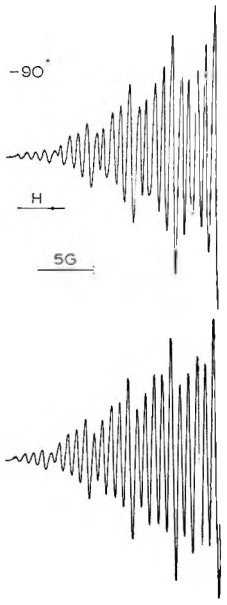



Figure 3.—Esr spectrum of the radical anion of III: upper, experimental spectrum at −90°; lower, calculated −90° spectrum using a line width of 0.30 G.

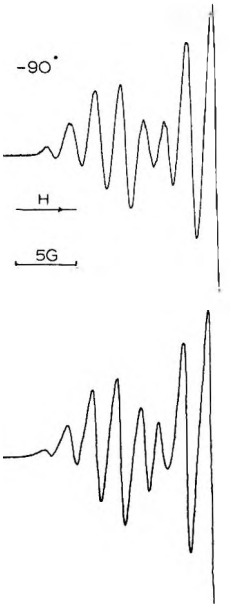


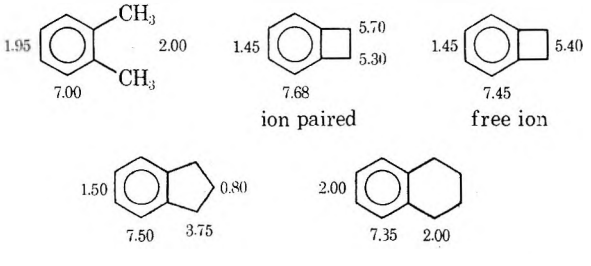

Figure 4.—Esr spectrum of the radical anion of IV: upper, experimental spectrum at −90°; lower, calculated −90° spectrum using a line width of 0.90 G.

Reduction of IV gave a dark blue solution and reversible spectra from −96 to −76°, with rapid decay of the signal above −70°. The spectra exhibited very little temperature dependency over this range. At −90° the spectrum could be simulated using the following hfsc: $A_{1,4}$ = 7.35, $A_{CH2\alpha}$ = 2.00 (4 H), and $A_{5,6}$ = 2.00. Splittings due to the β-methylene protons were not observed due to the large line widths (0.90 G at −90°). Attempts to resolve these splittings by use of a small modulation amplitude yielded little improvement. The experimental and simulated spectra for −90° are shown in Figure 4.

A summary of the results obtained for the benzene series using these reduction conditions is shown in Chart II. On the basis of the results of II, it appears

CHART II

HFSC AT −90° FOR COMPOUNDS I-IV REDUCED WITH POTASSIUM IN DME (90%) AND HMPA (10%)




that in this solvent system the dominant species in each reduction is the ion pair. It can be seen that the ring strain substantially perturbed the spin densities, most notably in the position α to the ring.

**Reduction with Potassium in DME (80%) and HMPA (20%). Initial Hydrocarbon Concentration, 0.01 *M*.**—In an attempt to obtain better resolution and provide more favorable conditions for free ion formation, the HMPA concentration was increased and the initial concentration of hydrocarbon was decreased. Under these conditions all the samples reduced to give dark blue solutions and exhibited a solvated electron peak. Metal splittings were not observed for any of these compounds.

Reduction of I gave weak spectra which were stable in the range of −70 to −90°. These spectra were essentially the same as obtained for I using the conditions of the previous section. The following hfsc were observed at −90°: $A_{1,4}$ = 7.00, $A_{CH_3}$ = 1.95, $A_{5,6}$ = 1.95.

Compound II was reduced under these conditions and spectra were recorded from −45 to −100°, exhibiting only the free ion. The spectra were reversible and temperature independent. At −90° the hfsc observed were $A_{1,4}$ = 7.40, $A_{CH_2}$ = 5.45 (4 H), and $A_{5,6}$ = 1.40.

Reduction of III yielded strong, reversible spectra from −50 to −90°. A large change in the hfsc and line-width alternation were observed, indicating a temperature-dependent interconversion process of some type. At −50 and −60° the spectra were similar to those obtained from the 0.1 *M* sample (see previous section) and had the following hfsc: $A_{1,4}$ = 7.55, $A_{CH_2\alpha}$ = 3.80 (4 H), $A_{CH_2\beta}$ = 0.80, $A_{5,6}$ = 1.55. Lowering the temperature from −65 to −80° resulted in the appearance of new lines and alternating line widths. At −85° the exchange process appeared to be completed, the lines being fairly sharp. The −85 and −90° spectra were essentially the same and could be simulated quite well using hfsc of $A_{1,4}$ = 7.25, $A_{CH_2\alpha}$ = 3.60, $A_{CH_2\beta}$ = 1.00, and $A_{5,6}$ = 1.50. These results and others obtained in THF–HMPA (see next section) indicate that the high temperature spectra (−50 to −60°) were due to the ion-paired species, while the low temperature spectra (−85 to −90°) were due to the free ion. Intermediate temperatures exhibited the interconversion between the ion pair and free ion.[24] The possible interconversion between various ion-pair conformations was not observed, as it was for II in potassium and DME,[15d] since one would expect such an interconversion to divide the α-methylene protons into

(24) M. C. R. Symons, *J. Phys. Chem.*, **71**, 172 (1967).

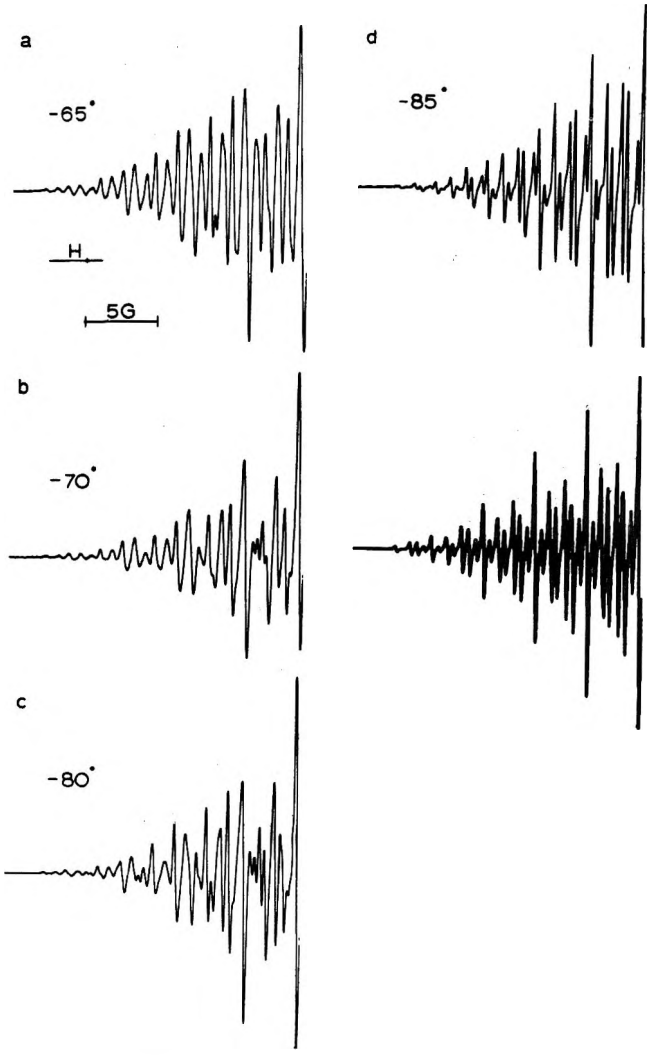



Figure 5.—Esr spectra for the radical anion of III: (a–d) experimental spectra obtained at the temperatures shown; (e) calculated −85° spectrum using a line width of 0.10 G.

two sets of two equivalent nuclei. Figure 5 exhibits the changes in the spectra with temperature for the radical anion of III prepared under these conditions.

Reduction of IV gave reversible, temperature dependent spectra from −50 to −95°. The spectrum width changed very little over this range. From −50 to −80° the spectra were essentially the same as observed for the 0.1 *M* sample (see previous section). At −90° and below additional hyperfine structure due to the β-methylene protons was observed. Also, a small amount of line broadening was observed for the external lines. Construction of a spin-state diagram failed to offer any reasons for the alternation. A reasonable fit for the −90° spectrum was obtained using hfsc of $A_{1,4}$ = 7.20, $A_{CH_2\alpha}$ = 2.15, $A_{CH_2\beta}$ = 0.30, and $A_{5,6}$ = 1.85. The experimental and simulated spectra at −90° are shown in Figure 6.

The results for the benzene series using these reduction conditions are depicted in Chart III at a temperature of −90°. At this temperature the species observed by esr appeared to be the free ion. Under these conditions, as with the 0.1 *M* samples discussed in the previous section, it can be seen that the spin densities are substantially perturbed as ring strain increased. The general trends for both sets of reduction conditions are seen to be in the same direction.

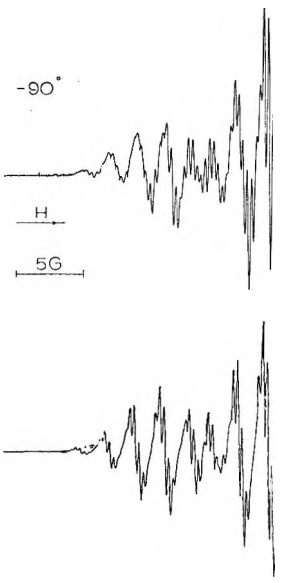
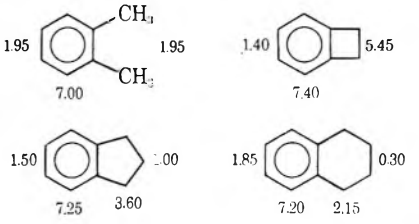



Figure 6.—Esr spectrum of the radical anion of IV: upper, experimental spectrum at −90°; lower, calculated −90° spectrum using a line width of 0.20 G.

CHART III

HFSC AT −90° FOR COMPOUNDS I–IV REDUCED WITH POTASSIUM IN DME (80%) AND HMPA (20%)




**Reduction with Potassium in THF (80%) and HMPA (20%). Initial Hydrocarbon Concentration, 0.01 *M*.**—Reductions were carried out in THF to lower the temperature range beyond that which was accessible in DME. The volume ratio and initial hydrocarbon concentration were the same as employed in the previous section. Reduction in all cases yielded dark blue solutions.

Compound I was not reduced using these conditions.

Reduction of II gave reversible spectra from −100 to −130°, the four methylene protons being equivalent over this temperature range, indicating formation of the free ion. At lower temperatues (−125° and below) anisotropic broadening was observed, and the spectrum width decreased slightly as the temperature was raised. The hfsc values were essentially temperature independent. At −110 the following values were observed: $A_{1,4}$ = 7.45, $A_{CH_2}$ = 5.50, $A_{5,6}$ = 1.40. A slight increase to $A_{1,4}$ = 7.49 and $A_{CH_2}$ = 5.60 was noted at −125°.

Compound III was reduced, yielding reversible spectra from −100 to −130°. With the exception of anisotropic line broadening at low temperatures the spectrum width and hfsc showed very little variation. At −110° the spectrum could be simulated quite well using hfsc of $A_{1,4}$ = 7.25, $A_{CH_2\alpha}$ = 3.60, $A_{CH_2\beta}$ = 1.00, and $A_{5,6}$ = 1.50. These spectra were the same as those obtained at −85° and below using the conditions of the previous section, indicating this species to be the

free ion. The ion-paired species was not observed under these reduction conditions.

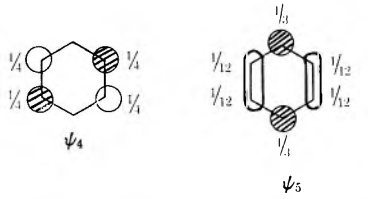
Using these conditions, IV reduced with some difficulty. A weak spectra which could be simulated with the hfsc shown in Chart III was obtained.

**Discussion of Ring Strain Effects.**—The results obtained for the benzene series reduced in DME and HMPA, summarized in Charts II and III, show the perturbation of spin density with ring strain. Examination of the charts indicates that as strain is increased the spin densities are strongly perturbed toward the strain ring. This means that the value of $A_{1,4}$ increases and $A_{5,6}$ decreases as strain is increased. It was desirable to obtain the esr spectra of these compounds in the absence of ion pairing, so that any interpretation of the results which invoked ion-paring perturbation of spin densities could be ruled out. It was felt that the values obtained for the 0.01 $M$ solutions in 80% DME and 20% HMPA (Chart III) are from the free ions, ion pairing being negligible at $-90°$. In any case, the hfsc obtained for the 0.1 $M$ and 0.01 $M$ samples in the different solvent systems indicate that an explanation other than ion-pair perturbation is required to adequately explain the results obtained.

The observed spin densities may be readily explained using the model of Finnegan–Streitwieser.[11,12] The reduction of an ortho-disubstituted benzene compound adds an electron to one of the two nearly degenerate benzene antibonding orbitals shown in Chart IV. It

CHART IV[a]

NEARLY DEGENERATE BENZENE ANTIBONDING ORBITALS




[a] The thatched circles represent p orbitals with the plus signs up while the empty circles represent p orbitals with the plus signs down. The number beside each orbital is the square of the coefficient.

has been demonstrated for many substituted benzenes that, if the substituent is electron donating, the extra electron will prefer the orbital which avoids the substituent. However, if the substituent is electron attracting, the extra electron will prefer the orbital which places maximum electron density next to the substituent.[25–29] The perturbation is never complete and generally the electron enters an orbital which is an admixture of the two orbitals. In the case of II, the extra electron will obviously enter $\psi_5$, which explains the large hfsc for the 1 and 4 positions. The hfsc were calculated using McConnell's[30] equation, employing a $Q$ value of 22.5 times the spin density at a given position in $\psi_5$, and the correlation was excellent. However, the hfsc values for the 1 and 4 positions of I, the least strained compound studied, were found to be 7.00 compared to 7.40 for BCB (Chart IV). It has been shown that the spin densities of several strained compounds could be correlated by making the carbon atoms $\alpha$ to the strained ring more electronegative.[15] Thus, in II the electron enters an antibonding orbital which weighs $\psi_5$ more heavily than in the case of I. In both cases the substituents are electron donating, causing the electron to prefer $\psi_5$; however, the increased electronegativity of the 1 and 4 positions of II results in a heavier weighting of $\psi_5$. For III and IV the effects of strain are less compared to II and the hfsc values for the 1 and 4 positions of 7.25 and 7.20 show a shift toward the weighting of $\psi_4$ and $\psi_5$ observed for I. This discussion assumes that the spin polarization mechanism for the 1 and 4 positions is unaffected by ring strain. Accordingly, the hfsc values for the benzene compounds at these positions which are directly proportional to spin density can be compared.

The use of the Finnegan–Streitwieser model discussed above provides a good qualitative explanation for the strain effects observed in the benzene series. For the corresponding naphthalene compounds[1] this model is placed on a more quantitive basis by using simple Hückel MO calculations and the more sophisticated Mulliken–Wheland–Mann technique.

One further point of interest is the difference in spin densities of I and IV. Formally both compounds are strain free and have two electron-donating alkyl groups. In the naphthalene series, there was little difference in the spin densities of 2,3-dimethylnaphthalene and 1,2,3,4-tetrahydroanthracene. This was taken to mean that two *o*-methyl groups can be treated the same way as two *o*-methylene groups in a strain free ring. This is apparently not so in the case of benzene. The difference in spin densities could be caused by some ion pairing which we have not removed totally but this seems unlikely. The difference in these two types of substituents is further demonstrated by the difference in chemical properties of these two molecules.[16]

**Registry No.** —I, 95-47-6; II, 694-87-1; III, 496-11-7; IV, 119-64-2.

**Acknowledgment.**—Financial support of this investigation by the National Science Foundation is gratefully acknowledged.

(25) T. R. Tuttle and S. I. Weissman, *J. Amer. Chem. Soc.*, **80**, 5342 (1958).
(26) H. L. Strauss and T. J. Katz, *J. Chem. Phys.*, **32**, 1873 (1960).
(27) J. Bolton and A. Carrington, *Mol. Phys.*, **4**, 497 (1961).
(28) T. R. Tuttle, *J. Amer. Chem. Soc.*, **84**, 2839 (1962).
(29) P. Rieger and G. Fraenkel, *J. Chem. Phys.*, **37**, 2795 (1962).
(30) H. M. McConnell and D. B. Chesnut, *ibid.*, **28**, 107 (1958).

# The Reactivity of *N*-Chloro- and *N*-Methylbenzenesulfonamide Anions with Methyl Methanesulfonate in Methanol[1]

JOHN H. BEALE[2]

*St. Petersburg, Florida 33702*

*Received June 19, 1972*

A comparison of the reactivity of *N*-chlorobenzenesulfonamide anion ($pK_a$ of the conjugate acid in methanol = 9.5) and *N*-methylbenzenesulfonamide anion ($pK_a$ = 15.5) with methyl methanesulfonate in methanol has shown that the weakly basic anion exhibits a second-order rate constant about five times larger than its *N*-methyl counterpart. On the basis of an extended Brønsted plot, a deceleration of 1000-fold would be expected. This finding represents a dramatic example of the $\alpha$ effect in displacement at saturated carbon.

The rate coefficient for the quantitative alkylation of *N*-chlorobenzenesulfonamide by methyl methanesulfonate is about five times larger than the rate coefficient for the alkylation of *N*-methylbenzenesulfonamide by methyl methanesulfonate. The Brønsted equation for general base catalysis, an often used correlation for reactivity, indicates that the *N*-chloro compound exhibits a 1500-fold increase in reactivity from expectations based on the basicity of the anion.[1] Clearly, the reason for enhanced reactivity must lie elsewhere.

It is the purpose of this paper to demonstrate that this finding is an example of the $\alpha$ effect in operation at saturated carbon.

The $\alpha$ effect which is the enhanced reactivity of certain nucleophiles and its importance in displacements on saturated carbon substrates remains an area of considerable interest. The common structural feature of these nucleophiles is "an electronegative atom containing one or more pairs of unsaturated electrons adjacent and attached to the nucleophilic site," in the description of Edwards and Pearson.[3]

There is, as yet, no thorough explanation of this effect; it appears to be separate from factors linking reactivity to polarizability, basicity, or solvation changes.[4]

Large, positive deviations from the extended Brønsted relation have been reported for $\alpha$ nucleophiles in reaction series where a high response to the basicity of the nucleophile (*i.e.*, nucleophilic attack at carbonyl carbon) is a recognized factor. The slope of the plot of the second-order rate constants *vs.* $pK_a$'s of the nucleophile conjugate acids approaches 1. To a lesser extent, these departures from expected behavior have been observed in nucleophilic displacements where polarizability of the nucleophile has been correlated with nucleophilicity (*i.e.*, displacements at saturated carbon).[5-7] The slope of the extended Brønsted plot here is about 0.5 for many reaction series.

Solvation changes have been ruled out as an explanation of the $\alpha$ effect by a study of Bruice and Gregory[4] of aminolysis of *p*-nitrophenyl acetate in acetonitrile.

The magnitude of the effect in the present study is a 1500-fold increase in the expected second-order rate constant at 25°. The Brønsted plot for the present report was developed in a previous paper.[8]

The kinetics of the alkylation reactions of some nitrogen nucleophiles with saturated carbon centers in methanol solution have been previously reported by Bunnett and Beale.[8] A technique for quantitatively coping with the complication of nucleophilic competition with methoxide ion was described.

The $pK_a$ of *N*-methylbenzenesulfonamide was determined by conductimetric studies[1] in methanol utilizing the high mobility of methoxide ion. Letting NH represent the free sulfonamide and $N^-$ its conjugate base, we may write

$$NH + CH_3OH \overset{K_a}{\rightleftharpoons} N^- + CH_3OH_2^+ \quad (1)$$

$$CH_3OH + CH_3OH \overset{K_s}{\rightleftharpoons} CH_3O^- + CH_3OH_2^+ \quad (2)$$

$$NH + CH_3O^- \overset{K_{eq}}{\rightleftharpoons} CH_3OH + N^- \quad (3)$$

It is easily shown that $K_a = K_s \cdot K_{eq}$. The $K_{eq}$ value was determined at 25° by perturbing the equilibrium 3 by additions of nitrogen acid, NH. The extent of the lowering of equivalent conductance was used to calculate $K_{eq}$ and derive $K_a$. Details are given in ref 1, pp 44–55. The $pK_a$ value of *N*-methylbenzenesulfonamide reckoned in this way is 15.5.

The $pK_a$ value of *N*-chlorobenzenesulfonamide was estimated to be 9.5 in absolute methanol. It was determined by titration to a glass electrode[9] of the stable salt in base[10] with acid in 50% aqueous methanol and then converted to absolute methanol by accepted relations.

$pK_a$ Values of NH compounds determined by titration in aqueous methanol and also by an independent conductivity measurement in absolute methanol are in good agreement.[1]

The slope of the extended Brønsted plot is taken to indicate the degree of bond formation in the transition state. In the study cited[8] it is 0.4.

The reactivities of *N*-methyl- and *N*-chloro-substituted benzenesulfonamides were compared to determine the magnitude of the effect in displacements at saturated carbon. The sizes and polarizabilities of methyl and chloro substituents are essentially equal.[11] One then expects that differences in reactivity will be solely electronic in nature.

(1) Based in part on the Ph.D. Thesis of J. H. Beale, Brown University, 1966. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society.

(2) 8880 15th Way North, St. Petersburg, Fla. 33702.

(3) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

(4) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 4400 (1967).

(5) R. G. Pearson and D. M. Edgington, *ibid.*, **84**, 4608 (1962).

(6) W. P. Jencks and J. Carriulo, *ibid.*, **82**, 1778 (1960).

(7) T. C. Bruice, A. Donzel, *et al.*, *ibid.*, **89**, 2106 (1967).

(8) J. F. Bunnett and J. H. Beale, *J. Org. Chem.*, **36**, 1659 (1971).

(9) M. Paabo, R. A. Robinson, and R. G. Bates, *J. Amer. Chem. Soc.*, **87**, 415 (1965).

(10) F. D. Chattaway, *Trans. Faraday Soc.*, **87**, 145 (1905).

(11) The group polarizations are 5.967 for Cl and 5.718 for $CH_3$. The van der Waals radii are 1.75 Å for Cl and 1.95 Å for $CH_3$. See F. Daniels and R. A. Alberty, "Physical Chemistry," Wiley, New York, N. Y., 1955, p 62; M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, p 600.

A comparison of the alkylation of *N*-methylbenzenesulfonamide and *N*-chlorobenzenesulfonamide by methyl iodide was attempted[1] to relate to the series previously reported.[8] The initial rate of alkylation of *N*-chlorobenzenesulfonamide anion by methyl iodide was rapid compared to methoxide reactivity. However, satisfactory rate data for the complete reaction were not obtained due to the consumption of chloramine in oxidizing iodide ion and other complicating reactions. Reduction of the iodine back to iodide before titration did not yield satisfactory kinetic results.

Attempted alkylations of *N*-hydroxy- and *N*,*N*-dimethylaminobenzenesulfonamides were studied briefly. The initial rates of formation of alkylation products seemed much faster than competitive alkylation of methoxide, but the main course of reaction led to decomposition products of the arylsulfonamide anions.[1]

## Experimental Section

Pseudo-first-order kinetic studies of the reaction of *N*-chlorobenzenesulfonamide with methyl methanesulfonate were conducted by following the formation of methylation product in the ultraviolet spectrum at 249 and 266 nm. An excess of methoxide ion (transparent in the uv) was present. Chloramine is stable in the presence of base. Since the compound is strongly acidic, no unconverted free acid was present and the concentration of nucleophile was exactly known.

The rate constants for the methylation of *N*-methylbenzenesulfonamide by methyl methanesulfonate (Tables I and II) were determined at several temperatures by two independent methods. The small values of absorbance change noted[1] by following this reaction in the uv (at 249 or 266 nm) and the uncertainty of the concentration of the nitrogen nucleophile owing to incomplete conversion of the weak acid to its anion made it desirable to determine the reactivity by another method. Thus, the reaction was followed in a separate series of second-order kinetic studies by analyzing for the disappearance of base. The true nucleophilic rate constant was obtained by adding controlled excesses of conjugate acid (NH) to methoxide solutions and determination of $k_N$ values as reported earlier.[8]

TABLE I

RATE DATA FOR REACTION OF *N*-METHYLBENZENESULFONAMIDE ANION WITH METHYL METHANESULFONATE IN METHANOL

| [$CH_3O^-$], *M* | [$CH_3OSO_2$-$CH_3$], *M* | [$CH_3NH$-$SO_2Ph$], *M* | $k_2$, $M^{-1}$ sec$^{-1}$ | Temp, °C |
|---|---|---|---|---|
| 0.0183 | 0.0500 | 0.132 | $1.43 \times 10^{-2}$ | 50.0 |
| 0.0183 | 0.0500 | 0.0764 | $1.47 \times 10^{-2}$ | 50.0 |
| 0.0183 | 0.0500 | 0.0419 | $1.31 \times 10^{-2}$ | 50.0 |
| 0.0183 | 0.0604 | 0.119 | $5.93 \times 10^{-3}$ | 39.8 |
| 0.0183 | 0.0604 | 0.092 | $5.5 \times 10^{-3}$ | 39.8 |
| 0.0183 | 0.0604 | 0.060 | $5.3 \times 10^{-3}$ | 39.8 |
| 0.0138 | 0.0572 | 0.120 | $9.55 \times 10^{-4}$ | 25.0 |
| 0.0130 | 0.0572 | 0.0805 | $9.50 \times 10^{-4}$ | 25.0 |

TABLE II

REACTION OF *N*-CHLORO- AND *N*-METHYLBENZENESULFONAMIDE ANIONS WITH METHYL METHANESULFONATE IN METHANOL

| Nucleophile | Temp, °C | $k_n$,[c] $M^{-1}$ sec$^{-1}$ | $\Delta H^{\pm}$, kcal mol$^{-1}$ | $\Delta S^{\pm}$, cal deg$^{-1}$ mol$^{-1}$ |
|---|---|---|---|---|
| *N*-Methylbenzenesulfonamide | 25 | $1.05 \times 10^{-3}$ [b] | 20.8 | −4.9 |
| | 25 | $9.55 \times 10^{-4}$ | | |
| | 39.8 | $5.68 \times 10^{-3}$ | | |
| | 50.0 | $1.44 \times 10^{-2}$ | | |
| *N*-Chlorobenzenesulfonamide[a] | 22.0 | $4.7 \times 10^{-3}$ | 15.2 | −19.7 |
| | 22.7 | $5.0 \times 10^{-3}$ | | |
| | 22.0 | $5.8 \times 10^{-3}$ | | |
| | 22.7 | $5.3 \times 10^{-3}$ | | |
| | 25.0 | $6.4 \times 10^{-3}$ [b] | | |
| | 30.3 | $9.4 \times 10^{-3}$ | | |
| | 30.3 | $9.9 \times 10^{-3}$ | | |
| | 33.0 | $1.2 \times 10^{-2}$ | | |
| | 33.6 | $1.4 \times 10^{-2}$ | | |

[a] Derived from pseudo-first-order kinetic rate constant, methyl methanesulfonate concentration, 0.15 *M*. [b] Extrapolated value. [c] $k_n$ Values corrected for volume expension of methanol.

## Results and Discussion

These data show that the stoichiometric excess of NH supresses the reaction of methoxide (the slower competitive reaction). The equilibrium constant for the reaction

$$CH_3O^- + PhSO_2NHCH_3 \underset{}{\overset{K_{eq}}{\rightleftharpoons}} CH_3OH + PhSO_2NCH_3^-$$

has been previously determined[1] and found to be rather small (*ca.* 10). For this reason, rather large molar ratios of the nucleophile conjugate acid (*N*-methylbenzenesulfonamide) to methoxide ion were employed in the second-order kinetic study followed by acid–base titration. This technique gives nearly constant $k_2$ values and the iteration required to find $k_N$ values as reported in ref 1 was not required. Within experimental error $k_2 = k_N$ in this work.

A plot of log $k_N$ *vs.* p$K_a$(NH) for the more extensive study of methyl iodide alkylations has a slope of 0.4. The rate constants for *N*-methylbenzenesulfonamide anion toward methyl iodide and methyl methanesulfonate, respectively, at 25° are $1.01 \times 10^{-3}$ and $1.05 \times 10^{-3}$ $M^{-1}$ sec$^{-1}$. By simple proportion, the reactivity of *N*-chlorobenzenesulfonamide toward methyl iodide is expected to be $6.1 \times 10^{-3}$ $M^{-1}$ sec$^{-1}$. Placement of this value on the extended Brønsted plot indicates a rate acceleration in alkylation of *N*-chlorobenzenesulfonamide of some 1500-fold.

This acceleration effect is one to two orders of magnitude larger than previous examples.[5]

The lower energy of activation of the *N*-chlorobenzenesulfonamide may be a general feature of $\alpha$ nucleophiles.[3,12] It indicates either that the energy of the reactant nucleophile is higher or the transition state is stabilized by partial bonding of the lone pair of electrons on the $\alpha$ atom. Both these explanations have been advanced,[4,7,13,14] but the data here do not allow a decision on the cause of the effect. The observations to date by others and this work are consistent with the notion of participation of $\alpha$ electrons to lower the energy of the transition state.

This work gives a positive demonstration that the effect operates not only in displacement reactions highly dependent on the basicity of the nucleophile (large Brønsted slope), but also in reactions where little bond formation may have occurred in the transition state (Brønsted slope 0.4).

**Registry No.**—*N*-Chlorobenzenesulfonamide, 80-16-0; *N*-methylbenzenesulfonamide, 5183-78-8; methyl methanesulfonate, 66-27-3.

(12) J. O. Edwards, 1967, private communication.

(13) C. K. Ingold, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965, 16S.

(14) K. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962).

# Formation and Alkylation of Lithium Enolates from Enol Phosphorylated Species[1]

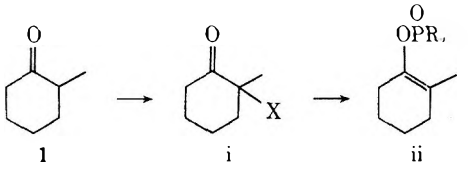
IRVING J. BOROWITZ,*[2] EDWARD W. R. CASPER, ROSALIE K. CROUCH, AND KWOK CHUN YEE

*Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York 10033*

*Received May 10, 1972*

The cleavage of vinyl phosphinates, vinyl phosphonates, or vinyl phosphates, derived from cyclic α-halo ketones, with methyl- or butyllithium smoothly yields the corresponding lithium enolate and inert phosphorus-containing by-products. Cleavage of enol triphenylphosphonium halides occurs but is complicated by the formation of biphenyl and triphenylphosphine as by-products and by the hydrolytic instability of the starting compounds. The lithium enolates thus formed can be regiospecifically monoalkylated on carbon in good yield. Polyalkylation occurs as a minor process mainly in methylation and is negligible for larger alkyl groups. Alkylation of several enolates, formed from ketones with lithium triphenylmethide, gives comparable results. A notable exception to the regiospecificity of the alkylations occurs with the less substituted lithium enolate of 2-methylcyclohexanone, which gives 2-methyl-2-butylcyclohexanone and not the desired 2-methyl-6-butylcyclohexanone. Corresponding methylation gives 2,6-dimethylcyclohexanone. The cleavage and alkylation of derivatives of acetone and butyraldehyde are described. The preparation of 2-methyl-6-bromocyclohexanone is discussed.

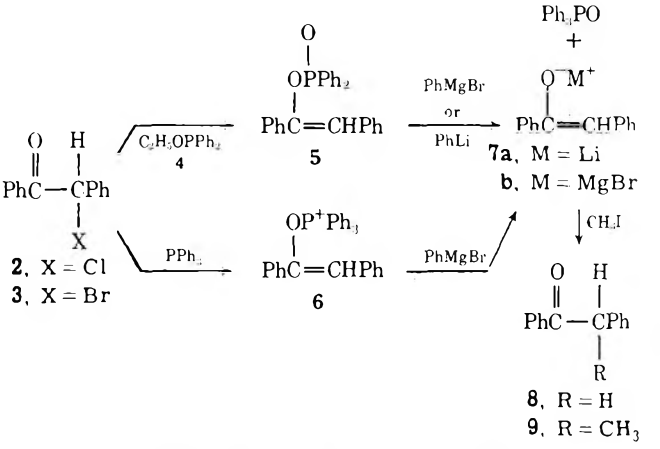
The conversion of α-halo ketones to vinyl phosphates occurs smoothly in high yield.[3,4] Vinyl phosphinates and phosphonates are also available from the reactions of α-halo ketones with alkyl diphenylphosphinites and dialkyl phenylphosphonites.[5] Less generally, some halo ketones can be converted to enol triphenylphosphonium salts upon reaction with triphenylphosphine (TPP).[6] This procedure avoids obtaining mixtures of the two possible enol derivatives of an unsymmetrical ketone as sometimes found in the formation of enol acetates[7] or enol trimethylsilyl ethers.[8,9]



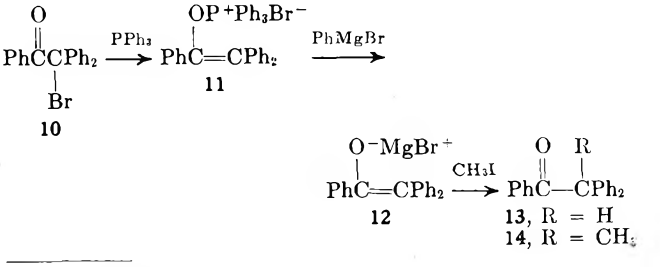

It was felt that enol phosphorylated species should be cleaved by strong bases to give lithium or magnesium enolates, which could then be monoalkylated.[8,10] The idea was originally based on the *in vivo* reactions of phosphoenol pyruvate with carbon dioxide[11a] or with sugar aldehydes,[11b] and more recently on the cleavage of α,α-disubstituted β-ketophosphonium salts with Grignard reagents to give ketones.[12] We now report the successful utilization of enol phosphorylated species along these lines.[13]

## Results and Discussion

Our initial results involved the cleavage of enol-phosphorylated derivatives of the 1,2-diphenylethylene system (Table I) with phenylmagnesium bromide or phenyllithium. The enol triphenylphosphonium chloride **6**, from α-chlorobenzyl phenyl ketone (**2**) and TPP,[6d] reacts with phenylmagnesium bromide or phenyllithium to give the enolate **7**. Biphenyl and TPP, formed as by-products, may arise *via* tetraphenylphosphonium halide and pentaphenylphosphorane[14] intermediates, as postulated in β-ketophosphonium salt reactions with Grignard reagents.[12]




The enol phosphonium bromide **11**, derived from **10**, reacted similarly.




(1) This investigation was supported by Grant No. 19,664 from the National Science Foundation. This is part 22 of the series Organophosphorus Chemistry. Taken in part from R. K. Crouch, Ph.D. Thesis, Yeshiva University, 1972. Presented in part at the Heteroatom Chemistry Meeting, London, Ontario, Sept 1970.

(2) To whom correspondence should be addressed.

(3) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

(4) (a) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967); (b) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *ibid.*, **36**, 3282 (1971).

(5) I. J. Borowitz and R. K. Crouch, *Phosphorus*, in press.

(6) (a) I. J. Borowitz, K. Kirby, P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971); (b) A. J. Speziale and R. D. Partos, *J. Amer. Chem. Soc.*, **85**, 3312 (1963); (c) R. D. Partos and A. J. Speziale, *ibid.*, **87**, 5068 (1965); (d) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *J. Org. Chem.*, **34**, 1595 (1969).

(7) (a) H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965); (b) H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967); (c) H. O. House and C. J. Blankley, *J. Org. Chem.*, **32**, 1741 (1967); (d) H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).

(8) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

(9) H. O. House, L. J. Czuba, M. Gall, and H. O. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(10) H. O. House, M. Gall, and H. O. Olmstead, *ibid.*, **36**, 2361 (1971).

(11) (a) J. L. Graves, B. Vennesland, M. F. Utter, and R. J. Pennington, *J. Biol. Chem.*, **223**, 551 (1956); (b) P. R. Srinivasan and D. B. Sprinson, *ibid.*, **234**, 716 (1959).

(12) T. Mukaiyama, R. Yoda, and I. Kuwajima, *Tetrahedron Lett.*, 23 (1969).

(13) I. J. Borowitz, E. W. R. Casper, and R. K. Crouch, *ibid.*, 105 (1971).

(14) (a) G. Wittig and G. Geissler, *Justus Liebigs Ann. Chem.*, **580**, 44 (1953); (b) G. Wittig and M. Rieber, *ibid.*, **562**, 187 (1949).

TABLE I

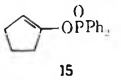
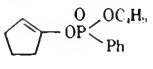
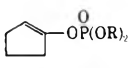
CLEAVAGE AND SUBSEQUENT REACTIONS OF PHOSPHORYLATED 1,2-DIPHENYLETHYLENES OR 11

| | | Yield, % | | | | |
|---|---|---|---|---|---|---|
| Compd | Conditions | Ketone | Methyl ketone | Biphenyl | $OPPh_3$ | $PPh_3$ |
| 6 | 1. PhMgBr,[a] THF[b] 2. $CH_3I$ added[b] | 1 | 36 | 16 | | 100 |
| 6 | 1. PhLi, THF[b] 2. $CH_3I$ added[c] | 4 | 86 | 64 | | 100 |
| 5 | 1. PhMgBr,[a] THF[b] 2. $CH_3I$ added[b] | 1 | 85 | | 98 | |
| 11 | 1. PhMgBr, THF (25°) 2. $CH_3I$ added, 25°, 16 hr | 27 | 46 | 34[d] | 95[d] | |

[a] Two equivalents. [b] Reflux 12 hr. [c] Reflux 5 hr. [d] From the acidification of the enolate in a separate experiment. Oxidation of anticipated $PPh_3$ may have occurred during work-up.

TABLE II

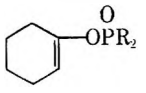
CLEAVAGE–ALKYLATION OF CYCLOPENTENYL DERIVATIVES WITH METHYL IODIDE[a,b]

| | | | Products | | | | |
|---|---|---|---|---|---|---|---|
| Compd | Organolithium (1 equiv) | Solvent |  |  |  |  |  |
|  15 | $CH_3Li$ | Glyme | 1 | 77 (76)[c] | 7 | 12 | 3 |
| | $CH_3Li$ | THF | 1 | 74 (72)[c] | 7 | 15 | 3 |
|  16 | $n$-$C_4H_9Li$ | Glyme | 5 | 64 | 16 | 9 | 6 |
|  17, R = $C_2H_5$ | $CH_3Li$ | Glyme | 12 | 78 | 4 | 6 | 0 |
| 18, R = $i$-$C_3H_7$ | $CH_3Li$ | Glyme | 14 | 62 | 9 | 12 | 3 |

[a] Cleavage for 5 min at room temperature; alkylation at 0° and quenched after 1 min. [b] All samples analyzed by vpc at 110° on 20% SE-30. Retention times: cyclopentanone, 2.3 min; 2-methylcyclopentanone (3.3); 2,2-dimethylcyclopentanone (3.8); 2,5-dimethylcyclopentanone (4.3). [c] Yield by vpc calibration curve.

TABLE III

CLEAVAGE–ALKYLATION OF CYCLOHEXENYL DERIVATIVES WITH METHYL IODIDE[a,b]



| | | | | Products | | |
|---|---|---|---|---|---|---|
| Compd | Organolithium (equiv) | Cleavage temp, °C | Solvent | 55 | 1 | 28 |
| 19, R = Ph | $n$-$C_4H_9Li$ (1.1) | 0 | Glyme–DMSO (2:1) | 1.6 | 90.4 (86)[c] | 8.0 |
| 20, R = Ph, $OC_4H_9$ | $CH_3Li$ (1.0) | 25 | Glyme | 14 | 81 (80)[c] | 5 |
| 21, R = $OC_2H_5$ | $CH_3Li$ (1.0) | 25 | Glyme | 32 | 63 | 5 |
| 21 | $CH_3Li$ (2.0) | 25 | Glyme | 13 | 79 (75)[c] | 8 |
| 22, R = O-$i$-$C_3H_7$ | $CH_3Li$ (1.0) | 25 | Glyme | 12 | 86 | 2 |

[a] Cleavage for 5 min. Alkylating solutions at 0° and alkylation step terminated after 5 min. [b] Vpc conditions for product analysis at 130° on 20% SE-30. Retention times: cyclohexanone (3.3 min); 2-methylcyclohexanone (4.5); 2,2-dimethylcyclohexanone (5.5); 2,6-dimethylcyclohexanone (6.0, genuine sample used). [c] Calibration curve (vpc).

The cleavage of vinyl phosphinate **5**, which was obtained from reaction of ethyl diphenyl phosphinite (**4**) with **2** (or **3**), phosphonates, or phosphates, was found to be best performed with methyl- or butyllithium in glyme to give a lithium enolate and a phosphine oxide, phosphinate, or phosphonate. Monoalkylation was achieved by rapid reaction of the enolate, which was added to alkyl iodide in glyme containing a small amount of dimethyl sulfoxide or hexamethylphosphoramide.[15]

The formation and the subsequent methylation of the lithium enolates of cyclopentanone and cyclohexanone are given in Tables II and III. Insignificant amounts of unalkylated ketone are obtained from the vinyl phosphinates **15**[5] and **19**,[4b] while the vinyl phosphates **17**,[4b] **18**, **21**, and **22** give these undesired by-products in greater yield. This may be due to a side reaction of the alkyllithium which displaces an alkoxide group from phosphorus.[16] The use of the diisopropyl vinyl phosphate **22** gives only slightly

(15) (a) P. Hudrlik, Ph.D. Thesis, Columbia University, 1968; (b) T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967); (c) P. A. Tardella, *Tetrahedron Lett.*, 1117 (1969).

(16) K. Sasse, Ed., "Organische Phosphorverbindungen, Methoden der Organischen Chemie (Houben-Weyl)," Vol. 12/1, Georg Thieme Verlag, Stuttgart, 1963, pp 32–43.

TABLE IV

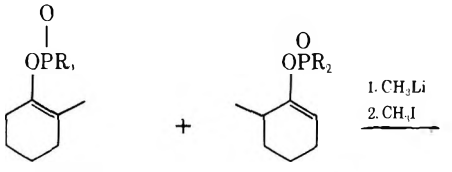
CLEAVAGE–ALKYLATION OF 2-METHYLCYCLOHEXENYL DERIVATIVES WITH METHYL IODIDE[a]

| Compd | Organolithium (equiv) | Cleavage conditions | Solvent | Alkylation Temp, °C | Alkylation Time, min | Products 1 | 28 | 29 | 30 | 31 |
|---|---|---|---|---|---|---|---|---|---|---|
| 27 | $n$-$C_4H_9Li$ (1.0) | c, d | Glyme | 25 | 2 | 2 | 91.5 (87)[b] | 0 | 6.5 | 0 |
| 27 | $n$-$C_4H_9Li$ (1.3) | c | Glyme–DMSO (2:1) | 0 | 5 | 25 | 60.8 | 0 | 14 | 0.2 |
| 26 | $n$-$C_4H_9Li$ (1.0) | e | Glyme | 0 | 2 | 7 | 80 | 2 | 11 | 0 |
| 23 | $CH_3Li$ (1.0) | e | Glyme | 0 | 1 | 18 | 76 | 3 | 3 | 0 |
| 24 | $CH_3Li$ (1.0) | e | Glyme | 0 | 1 | 17 | 0 | 76 (75)[b] | 3 | 4 |
| 25 | $n$-$C_4H_9Li$ (1.0) | f | Glyme | 0 | 1 | 13 | 60 | 5 | 22 | 0 |

[a] Analysis by vpc as in Table III. Retention time **30** (7.0 min), **31** (8.0). [b] By vpc calibration curve. [c] At 0° for 1 hr. [d] The use of $C_6H_5Li$ gave the product ratio 15:63 (**28**):2:15 (**30**):5. [e] At 25° for 20 min. [f] At 50° for 24 min.

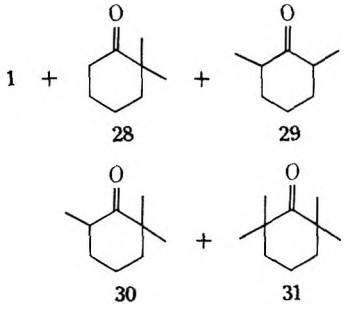
less cyclohexanone **55** than does the less hindered diethyl vinyl phosphate **21**.

The cleavage and methylation of the more and the less substituted isomeric vinyl phosphates of 2-methylcyclohexanone (**23**–**25**) and of other vinyl phosphorylated derivatives of the more substituted isomer (**26**, **27**[5]) are given in Table IV. The data indicates that butyllithium is more effective than is phenyllithium in the cleavage step and that an excess (0.3 equiv) of butyllithium results in overalkylation even though less ketone **1** is obtained.




**23**, R = $OC_2H_5$
**25**, R = O-*i*-$C_3H_7$
**26**, R = Ph, $OC_4H_9$
**27**, R = Ph

**24**, R = $OC_2H_5$

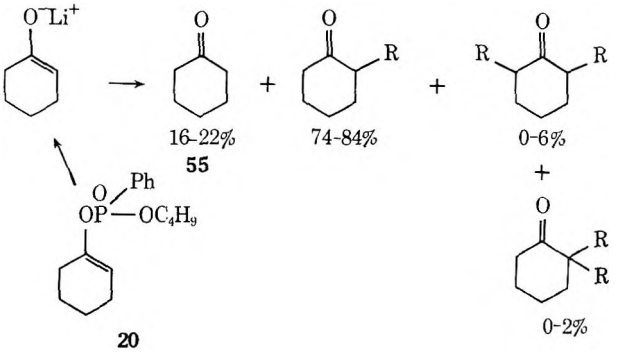



The alkylation of the lithium enolate of cyclohexanone generated from **20** with groups larger than methyl is summarized in Table V.

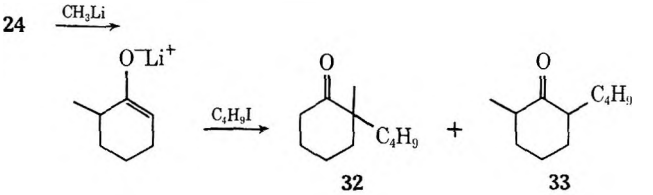
Reasonable yields of monoalkylated product are obtained with alkyl iodides although longer reaction times (1–4 hr) and elevated temperatures relative to methylation are required. Little or no dialkylation is noted for groups larger than ethyl.

Reaction of the lithium enolate of cyclohexanone, formed under kinetic control conditions[17] with butyl iodide, also gives mainly monoalkylation.

(17) (a) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); (b) the reagent of choice for kinetically controlled alkylations is now lithium diisopropylamide.[10]




An attempt to butylate the less substituted enolate formed from **24** gives the 2,2 isomer **32**[18] as the major product rather than **33**, the expected product. Thus




with alkylations considerably slower than methylation, equilibration of the less stable enolate of 2-methylcyclohexanone to the more stable one can occur faster than the alkylation. Thus far only methylation and benzylation[10] occur primarily on the less substituted side.

Extension of the cleavage–alkylation and direct alkylation sequences to cycloheptanone systems are given in Table VI. Little or no polyalkylation is observed for groups larger than methyl in the absence of excess base.

Several acyclic systems are thus monoalkylated. The vinyl phosphonate **37**[4b] of acetone is monobutylated to give 2-heptanone (**38**), and the dimethyl vinyl phosphate of butyraldehyde (**39**)[4b] is similarly converted to 2-methylbutyraldehyde (**40**).

**α-Alkyl-α′-bromo Ketones.**—The synthesis of less substituted vinyl phosphates such as **24** depends upon the availability of α-alkyl-α′-halo ketones such as 2-methyl-6-bromocyclohexanone (**42**). In principle pyr-

(18) P. Nedenskov, W. Taub, and D. Ginsburg, *Acta Chem. Scand.*, **12**, 1405 (1958).

TABLE V

ALKYLATION OF CYCLOHEXANONE LITHIUM ENOLATE WITH VARIOUS ALKYL HALIDES

| Precursor of enolate | Alkyl halide | Solvent | Time, hr | Temp, °C | Vpc conditions | Products: Cyclohexanone | Products: 2-Alkylcyclohexanone | Products: 2,2- or 2,6-Dialkylcyclohexanone |
|---|---|---|---|---|---|---|---|---|
| Cyclohexanone[a] | $n$-$C_4H_9I$ | Glyme | 4 | 90 | *b* | 18 | 74 | 2 (**56**)[h]<br>6 (**57**)[i] |
| **20**[e] | $C_2H_5I$ | Glyme | 0.5 | 50 | *c* | 22 | 76 | 2 |
| **20** | $i$-$C_3H_7I$ | Glyme–HMPA (2:1) | 20 | 90 | *d* | 16 | 84 | 0 |
| **20** | $n$-$C_4H_9I$ | Glyme | 4 | 90 | *b* | 22 | 78 | 0 |
| **20** | $n$-$C_4H_9I$ | Glyme–HMPA (2:1) | 4 | 90 | *b* | 17 | 83 | 0 |
| **20** | $n$-$C_4H_9Br$ | Glyme–HMPA (2:1) | 20 | 90 | *b* | 20 | 80 (67)[f] | 0 |
| | | | | | | 2-Methylcyclohexanone | 2-Methyl-2-butylcyclohexanone | |
| **24** | $n$-$C_4H_9I$ | Glyme | 24 | 90 | *g* | 31 (1) | 69 (**32**) | 0 |

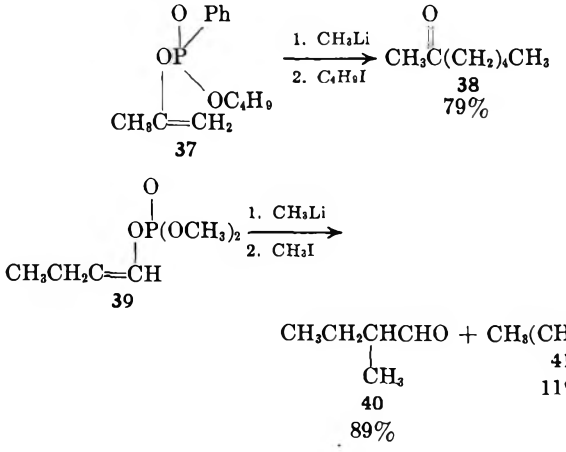
[a] Reacted with $LiCPh_3$ (1.0 equiv) for 1 min at 0°. [b] At 160°. [c] At 145°. [d] At 150°. All vpc work done on 20% SE-30 on Chromosorb W (10 ft × 0.25 in.) except for mixture from **24** (done on 10% SE-30). [e] Cleavage of **20** or **24** was done with $CH_3Li$ (1 equiv) at 25° for 15 min. [f] Distilled yield. [g] At 140°. [h] 2,2-Dibutylcyclohexanone. [i] 2,6-Dibutylcyclohexanone.

TABLE VI

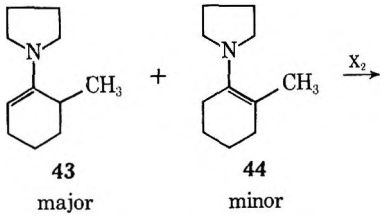
ALKYLATION OF CYCLOHEPTANONE LITHIUM ENOLATE WITH VARIOUS ALKYL HALIDES

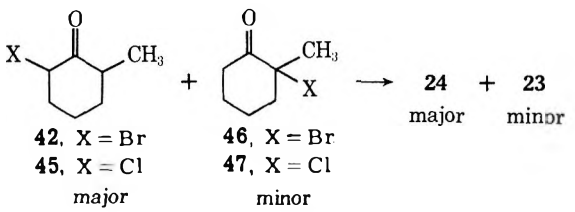
| Precursor of enolate | Alkyl halide | Solvent | Time, hr | Temp, °C | Vpc conditions | Products: Cycloheptanone | Products: 2-Alkylcycloheptanone |
|---|---|---|---|---|---|---|---|
| Cycloheptanone[a] | $n$-$C_4H_9I$ | Glyme | 16 | 90 | *b* | 42 (35) | 58 (**36**) |
| Diethyl cycloheptenyl phosphate (**34**) | $n$-$C_4H_9I$ | Glyme–HMPA (2:1) | 16 | 90 | *b* | 24 | 76 (**36**) |
| **34** | $n$-$C_4H_9Br$ | Glyme–HMPA | 96 | 90 | *b* | 51 | 49 (**36**) |
| **34** | $CH_2{=}CH(CH_2)_2Br$ | Glyme–HMPA | 88 | 90 | *c* | 39 | 61 |
| **34** | $CH_3I$ | Glyme–HMPA | 0.05 | 25 | *d* | 16 | 80[e] |

[a] Reacted with $LiCPh_3$ (1.0 equiv) for 5 min at 0°. [b] At 165°. [c] Programmed from 150° to 200° at 4°/min. Retention times: cycloheptanone (4.5 min); 2-(3′-butenyl)cycloheptanone (13.5). [d] At 160°. All vpc work on 20% SE-30 column as in Table V. [e] Also 2% dimethylcycloheptanone (2,2- or 2,6-) and 2% 2,2,6-trimethylcycloheptanone.




rolidino-2-methylcyclohexene, which exists as a 9:1 mixture of **43** and **44**,[19] should be convertible to **42** or **45**, and little **46** or **47**, by halogenation.[20a] In practice, a number of halogenation procedures on **43** and **44** involving bromine, sulfuryl chloride, *N*-bromosuccinimide, or *N*-chlorosuccinimide give primarily **46** or **47** and little of the desired **42** or **45**. Chlorination gives **45** and **47**.[20b,c] Bromination of **43** and **44** in acetic acid,[21] however, reproducibly gives **42**. Reaction of **42** with triethyl phosphite gives mainly **24** and very little **23**. Attempted debromination of **42** gives 2-methyl-2-cyclohexenone (**48**) and not 2-methyl-5-cyclohexenone (**49**).[22]




We find that the bromination of 2-methylcyclohexanone (in methanol) or bromination of its ethylene glycol ketal (**50**) gives mainly **46** and not **42**, contrary to

(19) (a) M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

(20) (a) Originally suggested by Professor G. Stork; (b) I. J. Borowitz, unpublished results; (c) L. Futrell, unpublished results, Yeshiva University.

(21) M. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, **33**, 3359 (1968).

(22) See E. W. Warnhoff, *ibid.*, **27**, 4587 (1962), for related phenomena.

previous work.[23] Attempts to brominate 2-methyl-6-carboxycyclohexanone (**51**)[24] give mixtures of **46** and **42** at best.

Attempts to extend enamine brominations to other unsymmetrical ketones are in progress.

## Experimental Section[25]

All solvents used were dried by distillation from calcium hydride, phosphorus pentoxide, or lithium aluminum hydride. Most reactions, including all alkylations, were conducted under prepurified nitrogen. Organic solutions were dried over anhydrous magnesium sulfate. Most of the vinyl phosphorylated species have been described,[3-6] as have their halo ketone precursors.[5,6a,6d]

**Butyl 1-cyclopentenyl phenylphosphonate** (16), 82% from the neat reaction of dibutyl phenylphosphonate (**52**) and 2-chlorocyclopentanone at 80° for 24 hr, had bp 135° (0.1 mm); ir (neat) 6.0 $\mu$; nmr ($CDCl_3$) $\tau$ 7.4–9.2 (m, 13, $CH_2$, $CH_3$), 6.10 (m, 2, $OCH_2$), 4.85 (m, 1, vinyl H), 2.0–2.8 (m, 5, phenyl); mass spectrum[26] (70 eV) *m/e* 280.1239 (calcd 280.1228). *Anal.* Calcd for $C_{16}H_{21}O_3P$: C, 64.24; H, 7.55. Found: C, 63.97; H, 7.69.

**Butyl 1-cyclohexenyl phenylphosphonate** (20), 86% from **52** and 2-chlorocyclohexanone in $CHCl_3$ at reflux for 36 hr, had bp 130° (0.05 mm); ir (neat) 6.0 $\mu$; nmr ($CDCl_3$) $\tau$ 4.64 (m, 1, vinyl) and other peaks as for **16**; mass spectrum[26] (70 eV) *m/e* 294.1411 (calcd 294.1385). *Anal.* Calcd for $C_{16}H_{23}O_3P$: C, 65.28; H, 7.88. Found: C, 63.48 (could not be improved); H, 8.08.

**Butyl 1-(2-methyl)cyclohexenyl phenylphosphonate** (26), 91% from **52** and 2-methyl-2-chlorocyclohexane (**47**) in $CHCl_3$ at reflux for 90 hr, had bp 148–150° (0.1 mm); ir (neat) 6.05 $\mu$. *Anal.* Calcd for $C_{17}H_{25}O_3P$: C, 66.18; H, 8.17. Found: C, 66.08; H, 8.25.

The following vinyl phosphates were synthesized from the appropriate halo ketone and triisopropyl phosphite (**53**) in 2-propanol. Their nmr spectra exhibited $\tau$ 7.5–8.2 (CH, $CH_2$), 8.6–8.7 (d, $CH_3$), 5.35–5.46 (m, OCH).

**Diisopropyl cyclopentenyl phosphate** (18), 49% from **53** and 2-chlorocyclopentanone (100°, 18 hr), had bp 62–64° (0.05 mm); ir (neat) 6.05 $\mu$; nmr ($CDCl_3$) $\tau$ 4.75 (m, 1, vinyl). *Anal.* Calcd for $C_{11}H_{21}O_4P$: C, 53.21; H, 8.53. Found: C, 53.03; H, 8.62.

**Diisopropyl cyclohexenyl phosphate** (22), 81% from **53** and 2-chlorocyclohexanone (25°, 18 hr), had bp 95–97° (0.1 mm); ir (neat) 5.95 $\mu$; nmr ($CDCl_3$) $\tau$ 4.55 (m, 1, vinyl). *Anal.* Calcd for $C_{12}H_{23}O_4P$: C, 54.94; H, 8.84. Found: C, 54.71; H, 8.80.

**Diisopropyl 1-(2-methyl)cyclohexenyl phosphate** (25), 57% from **53** and **47** (90°, 48 hr), had bp 108–110° (0.03 mm); ir (neat) 6.0 $\mu$; nmr ($CDCl_3$) $\tau$ 7.6–8.5 (m, 11, $CH_2$, vinyl $CH_3$). *Anal.* Calcd for $C_{13}H_{25}O_4P$: C, 56.51; H, 9.09. Found: C, 56.75; H, 9.07.

**Diethyl 1-(6-methyl)cyclohexenyl phosphate** (24), 78% from crude 2-methyl-6-bromocyclohexanone, **42** (*ca.* 0.15 mol), and triethyl phosphite (25 g, 0.162 mol) in $CHCl_3$ at reflux for 24 hr, had bp 100–103° (0.07 mm); ir (neat) 6.0 $\mu$; nmr ($CCl_4$) $\tau$ 5.82 (m, 4, $OCH_2$), 4.58 (m, 0.85–1, vinyl H), 8.9 (d, 3, $CH_3CH$, $^3J$ = 7 Hz); vpc (5% Carbowax on Chromosorb W, Teflon–aluminum column) one peak with retention time of 12.2 min at *ca.* 120° (temperature-programmed run). However, the isomeric **23** or a 1:1 mixture of **23** and **24** gave the same peak, *i.e.*, no separation. *Anal.* Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.53. Found: C, 53.07; H, 8.77.

**Diethyl 1-(2-methyl)cyclohexenyl phosphate** (23), 69% from TEP and 2-methyl-2-chloro (or bromo) cyclohexanone,[4a] had bp 90–92° (0.1 mm) [lit.[4a,27] bp 91–92° (0.1 mm)]; ir (film) 5.88 $\mu$; nmr ($CDCl_3$) $\tau$ 8.32 (broad s, 4.6, includes vinyl $CH_3$) and other peaks as for **24**.

**General Procedure for the Cleavage–Alkylation of Enol Phosphorylated Species.**—To the enol phosphorylated species (0.01 mol) in glyme (50 ml) containing a trace of triphenylmethane,[7] alkyl- or aryllithium (0.01 mol unless otherwise specified, 0.50–2.5 *M* in ether or hexane) was added under nitrogen by syringe until a red color persisted. The solution was stirred for the length of time specified and at the given temperature in the tables. The resultant enolate was then added under nitrogen to a solution of the alkylating agent in glyme, glyme–HMPA, or glyme–DMSO (10 ml of glyme, 5 ml of DMSO or HMPA) at the specified temperature. After a given reaction time, hydrochloric acid (1 *N*, 50 ml, 0.05 mol) was added. The organic layer, combined with diethyl ether extracts (3 × 50 ml) of the aqueous layer, was washed with saturated $NaHCO_3$ and dried ($MgSO_4$) and the solvent was distilled at 760 mm to give a residue which was dissolved in hexane and analyzed by vpc. Phosphinate or phosphonate by-products were removed during the acidic work-up while phosphine oxides either remained as hexane-insoluble residue or could be removed by filtration through alumina (especially for preparative scale reactions). The identity of the alkylated products was either assumed from known vpc retention times,[15a] by comparison with genuine samples or as follows. The vpc product analyses assumed equal thermal conductivity detector response for the parent and alkylated ketones in a reaction mixture. This commonly used procedure was shown to be valid or to involve small error in a number of cases by comparison with known samples of unalkylated and alkylated ketone. The yield of the major product in some runs was also estimated by vpc calibration curves using known samples of 2-methylcyclohexanone, 2,6-dimethylcyclohexanone, 2-methylcycloheptanone, 2-ethylcyclohexanone,[19a] and 2-isopropylcyclohexanone.[28]

**Reactions of Enol Triphenylphosphonium Bromide 11 and Related 1,2-Diphenylethylene Phosphorylated Species.**—The cleavage of **11** with phenylmagnesium bromide followed by methylation gave methyldiphenylacetophenone (**14**, 46%): mp 90–92° (lit.[29] mp 91–92°); ir ($CHCl_3$) 5.99 $\mu$; uv max (95% $C_2H_5OH$) 250 nm (log $\epsilon$ 4.05) [lit.[30] uv max 245 (4.0)]; nmr ($CDCl_3$) $\tau$ 2.82 (s, 3, $CH_3$), 2.25, 2.35 (d, *ca.* 2, ortho H of PhCO), 2.7 (m, *ca.* 13, phenyl H); mass spectrum (70 eV) *m/e* 286 ($M\cdot^+$), 271 ($PhCOC^+Ph_2$), 183 ($Ph_2C^+OH$), 166 ($Ph_2C^+$), 105 ($PhCO^+$), 77 ($C_6H_5^+$), metastable peak at *ca.* 60 for 105 → 77.

Similar reaction of enol phosphonium salt 6[6d] or vinyl phosphinate **5** gave $\alpha$-methylbenzylphenyl ketone (**9**): ir ($CHCl_3$) 5.94 $\mu$; nmr ($CDCl_3$) $\tau$ 5.34 (q, 1, methine H, $^3J$ = 7 Hz), 8.49 (d, 3, $CH_3$, $^3J$ = 6.9 Hz); mass spectrum (70 eV) *m/e* 210 ($M\cdot^+$), 195 ($PhCOCH^+Ph$), 178 ($PhCH_2^+$), 105 ($PhCO^+$, $PhCH^+CH_3$), 91, 77. No dimethylated ketone was found.

**2-Butylcyclohexanone** (**54**).—The cleavage of butyl cyclohexenyl phenylphosphonate (**20**, 0.05 mol) with methyllithium at 25° for 15 min, followed by reaction with butyl iodide in glyme–HMPA for 4 hr at 90°, gave 2-butylcyclohexanone (**54**)–cyclohexanone (**55**) in 80:20 ratio (vpc retention time 9.0 min, 1.5 min at 160° on 20% SE-30 on Chromosorb W in a 10 ft × 0.25 in. column). Distillation gave **54** (5.2 g, 0.032 mol, 64%): bp 89–92° (12 mm) [lit.[28] bp 86–96° (15–20 mm)]; vpc (as above) 99% one peak; 2,4-DNP (orange needles) mp 110–112° (lit.[28] mp 112–113°).

**2-Methyl-2-butylcyclohexanone** (**32**).—Cleavage and alkylation of **24** (Table V) with methyllithium and butyl iodide gave 2-methyl-2-butylcyclohexanone (**32**): vpc at 165° (20% SE-30) 22–3% **1**, 65–69% **32**, 0–13% **24** depending upon run; ir (film) 5.87 $\mu$, similar but nonidentical spectrum with that of **33**; nmr ($CCl_4$) $\tau$ 7.8, 8.5–8.9 (m, *ca.* 15), 9.3, 9.4 (part of butyl methyl), and 9.02, which was shifted to 9.5 (s, 3, $C_2CH_3$) by 0.033 equiv of $Pr(DPM)_3$.[31] The 2,4-DNP of a vpc-collected sample had mp 142–144° (lit.[18] mp 144°).

**2-Methyl-6-butylcyclohexanone** (**33**).—To 2-methyl-6-carboethoxycyclohexanone (4.60 g, 0.025 mol) in dry toluene (30 ml) was added NaH [0.60 g, 0.025 mol, washed with petroleum ether

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

(24) Related to the method for the conversion of 2-carboxyeyclohexanone to 2,2-dibromocyclohexanone: E. J. Corey, *J. Amer. Chem. Soc.*, **77**, 3297 (1953).

(25) The instrumental techniques used have been recorded.[4b,6a] Mass spectra were recorded on Hitachi RMU-6 mass spectrometers at the Einstein Medical College or at Columbia University.

(26) High-resolution mass spectra were done by R. Foltz, Battelle Memorial Institute, Columbus, Ohio, on an MS-9 mass spectrometer under NIH contracts 69-2226 and 71-2483.

(27) B. A. Arbusov, V. S. Vinogradova, and N. A. Polezhaeva, *Dokl. Akad. Nauk SSSR*, **121**, 641 (1958); *Chem. Abstr.*, **53**, 1180 (1959).

(28) S. Ramseyer (Dowd), Ph.D. Thesis, Columbia University, 1962.

(29) M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 1458 (1951).

(30) (a) H. Rinderknecht, *J. Amer. Chem. Soc.*, **73**, 5770 (1951); (b) M. J. Kamlet, Ed., "Organic Electronic Spectral Data," Vol. 1, Interscience, New York, N. Y., 1960.

(31) J. Britts, G. E. Frost, F. A. Hart, G. P. Moss, and M. L. Staniford, *Chem. Commun.*, 749 (1970).

(bp 30–60°) to remove oil]. The mixture was heated at reflux for 3 hr after the initial exothermic reaction subsided, and then cooled. Butyl bromide (3.7 g, 0.027 mol) in toluene (10 ml) was added over 10 min and the resultant mixture was heated at reflux for 17 hr. The usual work-up gave a yellow oil [3.9 g crude, vpc (at 240° on 20% SE-30) 62% alkylated β-keto ester, 38% starting β-keto ester]. The crude product was hydrolyzed with NaOH (4.0 g, 0.1 mol) in $C_2H_5OH$–$H_2O$ (100 ml each), acidified with dilute HCl, and extracted with ether to give 2-methyl-6-butylcyclohexanone (*ca.* 2.3 g, 0.007 mol, 29%): bp 85° (2.5 mm); ir (film) 5.87 μ; nmr ($CCl_4$) τ 7.5–9.35 (m, 20) with apparent doublet at 9.06 ($J$ = 6 Hz) which was shifted to 9.64 (d, 3, $CH_3CH$, $J$ = 6 Hz) with 0.038 equiv of $Pr(DPM)_3$. In comparison the nmr ($CCl_4$) of 2-methylcyclohexanone has τ 9.06 (d, 3, $CH_3$, $J$ = 6 Hz). No separation of **32** and **33** by vpc was noted on 20% SE-30 (175–217°) or 5% Carbowax (100–135°) columns under isothermal or temperature-programmed conditions. *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.40; H, 11.94. The 2,4-DNP of **33** formed with difficulty (in contrast to that of **32** which formed readily) and was an oil: uv max (95% $C_2H_5OH$) 363 and 228 nm; ir (film) 6.15 μ (C=N); tlc (silica gel $HF_{254}$) $R_f$ 0.3 (ether–hexane) while 2,4-DNPH had $R_f$ 0; uv max (95% $C_2H_5OH$) 350, 260 nm; nmr ($CDCl_3$) τ −1.2 (s, 1, NH), 0.8 (d, 1, aryl $H_c$), 1.6–2.1 (AB quartet, 2, aryl $H_{a,b}$), 6.8–9.3 (m, 20).

**2-Butylcycloheptanone** (**36**)[32] was collected by vpc (on 20% SE-30) from the cleavage–alkylation of **34**[4b] (Table VI): mass spectrum (20 eV) $m/e$ (rel intensity) 168 ($M^{\cdot+}$, 37), 153 ($M - CH_3$, 3), 112 [$CH_2{}^+(CH_2)_2CH\cdot-C_4H_9$, 56], 111 [$^+O{\equiv}CC(C_4H_9){=}CH_2$, 33], 97 ($C_6H_9O$, 100), 55 ($^+O{\equiv}CC{=}CH_2$, 89); calcd M + 1 for $C_{11}H_{20}O$, 12.1; found, 12.2.

**2-Methylbutyraldehyde** (**40**) was separated from butyraldehyde [out of the mixture resulting from the cleavage (0°, 1 min), alkylation (25°, 1 min) of **39**] by its greater solubility in ether. It was identified by its vpc retention time (5.1 min at 85° on 20% SE-30) which was identical with that of a genuine sample and by conversion to its 2,4-DNP: mp 120–121°; mmp 121–122° with that of a genuine sample (lit.[33] mp 120°).

(32) W. von E. Doering and C. F. Hiskey, *J. Amer. Chem. Soc.*, **74**, 5688 (1952).

(33) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1967, p 320.

**2-Heptanone** (**38**).—The lithium enolate of acetone, generated from the butyl phenylphosphonate **37**, was alkylated with butyl iodide for 3 hr at 25° to give **38** (79% as determined by a vpc calibration curve using genuine samples). No polyalkylated material was detected. The vpc of **38** had a retention time of 5.8 min at 130° on 20% SE-30. The yield of recovered acetone could not be determined because of its nonseparation from other volatile components (vpc).

**2-Methyl-6-bromocyclohexanone** (**42**).—To pyrrolidino-6-methylcyclohexene (**43**, 25.0 g, 0.15 mol) in $CHCl_3$ (200 ml) and glacial acetic acid (90 ml), cooled to 0–5° in a salt–ice bath, bromine (28.0 g, 0.15 mol) in $CHCl_3$ (50 ml) was added dropwise with stirring under nitrogen. The reaction temperature was kept below 5° during the addition and for another 10 min, water (200 ml) was added and the reaction mixture was poured into saturated $NaHCO_3$ solution (400 ml). The organic layer was washed with water (3 × 200 ml), dried ($MgSO_4$), and usually directly converted to vinyl phosphate **24**. Removal of the solvent at 25° *in vacuo* gave a dark red oil: nmr ($CCl_4$) τ 8.91 (d, *ca.* 3, $CH_3$, $J$ = 6.5 Hz), 7.0–8.4 (m, 7, $CH_2$), 5.22 (m, *ca.* 1, CHBr). Yields were *ca.* 80% of mixtures of 8–9 parts of **42** and 1–2 parts of 2-methyl-2-bromocyclohexanone (**46**). Rearrangement of **42** to **46** occurred in part upon attempted vpc and slowly at 25° (complete conversion in 24 hr). Reaction of **42** with lithium bromide, lithium carbonate, dimethylformamide, or collidine gave only 2-methylcyclohexenone, 2,4-DNP mp 208° (lit.[34] mp 207.5–208.5°).

**Registry No.**—**5**, 30758-39-5; **6**, 30758-40-8; **9**, 2042-85-5; **11**, 26709-97-7; **14**, 36504-01-5; **15**, 30758-45-3; **16**, 36504-02-6; **17**, 30842-23-0; **18**, 36504-03-7; **19**, 30758-41-9; **20**, 30758-44-2; **21**, 4452-32-8; **22**, 36504-04-8; **23**, 30908-58-8; **24**, 30908-59-9; **25**, 36504-06-0; **26**, 36547-04-3; **27**, 30758-42-0; **32**, 1197-78-0; **33**, 36504-08-2; **33** DNP, 36504-09-3; **34**, 31327-27-2; **36**, 36504-11-7; **42**, 36504-12-8; cyclohexanone lithium enolate, 21300-30-1; 2-methylcyclohexanone lithium enolate, 13670-83-2; cycloheptanone lithium enolate, 36504-15-1.

(34) E. W. Warnhoff and H. P. Landerl, *J. Amer. Chem. Soc.*, **75**, 494 (1953).

# Chirality and Structure of Organosilicon Radicals

L. H. SOMMER* AND L. A. ULLAND

*Department of Chemistry, University of California, Davis, California 95616*

*Received February 15, 1972*

Pyramidal structure for triorganosilyl radicals ($R_3Si\cdot$) in general is indicated by chirality studies on five optically active organosilicon systems containing asymmetric silicon. Reactions of five different optically active silanes, $R_3Si^*H$, with carbon tetrachloride, catalyzed by benzoyl peroxide, gave optically active $R_3Si^*Cl$ compounds. Progressively greater dilution of the carbon tetrachloride with benzene or cyclohexane demonstrated the capacity of the α-NpPhMeSi·* radical to invert. Also, for reasons presently unknown $Ph_3SiSi^*(Ph)(Me)H$ gave optically inactive $Ph_3SiSi^*(Ph)(Me)Cl$.

Recent studies by Brook[1] and Kumada[2] have provided evidence that the α-naphthylphenylmethylsilyl radical as generated in reactions 1 and 2 below is chiral and nonplanar. In these studies $R_3Si^*Cl$ is optically active α-NpPhMeSi*Cl.

$$R_3Si^*H + CCl_4 \xrightarrow[\Delta]{Bz_2O_2} R_3Si^*Cl + CHCl_3 \quad (1)$$

$$R_3Si^*COCH_3 + h\nu \longrightarrow R_3Si\cdot{}^* + \cdot COCH_3 \xrightarrow{CCl_4} R_3Si^*Cl + CH_3COCl \quad (2)$$

In both reactions the optically active organosilicon reactants gave the product chlorosilane, $R_3Si^*Cl$, with *retention* of configuration. For reactions 1 and 2, respectively, optical purities of product $R_3Si^*Cl$ were 86 and 64%.

However, both of the above studies were limited to generation and reaction of the same radical, α-NpPhMeSi·, and we wish now to report results which demonstrate (a) chirality for a wide variety of monosilane radicals; (b) nonchirality or rapid inversion for a disilane radical; (c) capacity of the α-NpPhMeSi·* radical to invert under conditions of progressively greater dilution of the $CCl_4$ in reaction 1 by benzene and cyclohexane.

Results for reaction 1 using a wide variety of $R_3Si^*H$ compounds and pure $CCl_4$ as solvent–reactant are reported in Table I. References listed in Table I

(1) A. G. Brook and J. J. Duff, *J. Amer. Chem. Soc.*, **91**, 2118 (1969).

(2) H. Sakurai, M. Murakami, and M. Kumada, *ibid.*, **91**, 319 (1969).

TABLE I
RADICAL REACTIONS OF $R_3Si^*H$ WITH $CCl_4$ TO GIVE $R_3Si^*Cl$

| No. | $R_3Si^*H$ reactant | $R_3Si^*H$,[a] $[\alpha]D$, deg | $R_3Si^*Cl$,[a] $[\alpha]D$, deg | $R_3Si^*Cl$,[b] optical purity, % | Ref |
|---|---|---|---|---|---|
| 1 | α-NpPhMeSi*H | +35.0 | −5.9 | 92 | 3 |
| 2 | neo-$C_5H_{11}$PhMeSi*H | +1.6 | +4.6[d] | 100 | 4 |
| 3 | $Ph_F$PhMeSi*H[c] | +3.5 | −16.0[d] | 84 | 5 |
| 4 | α-NpPh$_F$MeSi*H[c] | +22.4 | +25.7[d] | 90 | 5 |
| 5 | $Ph_2$CHPhMeSi*H | +3.1 | +13.6 | 100 | 4 |
| 6 | $Ph_3$SiSi*(Ph)(Me)H | +7.3 | 0.0 | 0 | 6 |

[a] All rotations taken in pentane unless otherwise noted. [b] First five reactions proceed with predominant *retention* of configuration. [c] $Ph_F$ is perfluorophenyl, $C_6F_5$. [d] Rotation in $CCl_4$.

report the syntheses, optical rotations, and correlations of configuration for the $R_3Si^*H$ reactants and $R_3Si^*Cl$ products.[3-7]

All of the reactions in Table I were run in refluxing $CCl_4$ using benzoyl peroxide as the initiator. Reaction times required for complete reaction, as monitored by glpc, varied from 0.25 to 24 hr. This reaction was chosen for study because of the moderately long chain lengths (50–80) and lack of side reactions.[8]

For reactions 1–5 (Table I) the optical purities and signs of rotation show predominant *retention* of configuration and high stereospecificity. In these reactions, then, the organosilicon radicals maintain chirality. Thus, these radicals prefer a pyramidal geometry and their rate of reaction with $CCl_4$ in pure $CCl_4$ solvent–reactant is faster than their rate of inversion. Since the structural variation of the monosilyl radicals in reactions 1–5 (Table I) is fairly wide, it is reasonable to conclude that *a pyramidal geometry generally obtains for* $R_3Si\cdot$ and that optically active $R_3Si\cdot^*$ can maintain chirality.

Previously, esr[9,10] and ir[11,12] data have been interpreted as indicating a pyramidal structure for monosilane radicals. Thus, the present data provide important confirmation of this interpretation and establish beyond any doubt the general pyramidal nature of such radicals.

Since $Ph_3SiSi^*(Ph)(Me)H$ is a relatively reactive silane with $CCl_4$ and since the other silanes have configuration stability under the reaction conditions, it seems highly unlikely that $Ph_3SiSi^*(Ph)(Me)H$ can, itself, be racemized by the reagent prior to formation of the chlorosilane.

Concerning reaction 6 in Table I, formation of racemic $R_3Si^*Cl$ was shown not to be due to racemization of initially optically active chlorosilane. The latter was found to be optically stable under the reaction conditions. Thus, the lack of optical activity in the product must be due either to a preferred planar geometry for the disilane radical or to rapid inversion of its pyramidal geometry. There is some esr evidence for preferred planar geometry for disilane radicals,[9] but more extensive study is certainly necessary. We consider that the result of reaction 6 suggests, but certainly does not prove, that the disilanyl radical is planar. If this radical were pyramidal, its rate of inversion might exceed its rate of reaction with $CCl_4$ and thus give the observed result. For example, see the studies discussed below.

In our next experiments we investigated the point just raised concerning possible competitive rates of inversion and reaction for chiral $R_3Si\cdot^*$. Reaction rates of the radicals were decreased by progressive dilution of the $CCl_4$ with benzene and the optical purity of the product $R_3Si^*Cl$ was determined by trapping the chloro silane by reaction with neopentyllithium. The coupling product was separated from the unreacted $R_3Si^*H$, and from the specific rotation of the $R_3Si^*C_5H_{11}$[4] the optical purity of the product was calculated.

The two-step stereoreaction sequence is given in eq 3 and the second step proceeds with excellent stereospecificity[4] and inversion of configuration.[4]

$$(+)\text{-}R_3Si^*H + CCl_4 \xrightarrow{Bz_2O_2} (-)\text{-}R_3Si^*Cl \xrightarrow[Et_2O]{C_5H_{11}Li} (+)\text{-}R_3Si^*C_5H_{11} \quad (3)$$

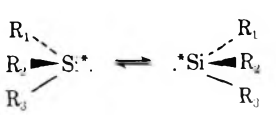
Results of these studies are reported in Table II.

TABLE II
EFFECTS OF BENZENE DILUTION ON THE STEREOSPECIFICITY OF REACTION OF (+)-$R_3Si^*H$ WITH $CCl_4$

| % $CCl_4$ (v/v) | $[\alpha]D$, $R_3Si^*C_5H_{11}$, deg | Optical purity, % |
|---|---|---|
| 100 | +21.4 | 92 |
| 75 | +20.1 | 87 |
| 50 | +18.4 | 79 |
| 25 | +15.3 | 66 |
| 10 | +10.4 | 45 |

From Table II it is clear that there is a dramatic decrease in product optical purity as the $CCl_4$ is diluted with benzene. Therefore, inversion of the chiral radical can compete with reaction. To eliminate the possibility of a specific solvent effect with benzene, such as radical complexation, which would lower the radical's reactivity and perhaps favor its racemization prior to reaction, a second series was performed with cyclohexane. The decrease in optical purity on dilution with cyclohexane paralleled the results given in Table II.

We conclude that the rates of eq 4 below can be competitive with reaction of the radical in certain cases.



(4)

## Experimental Section

**A. Radical Reactions of Optically Active Organosilanes with $CCl_4$. Reaction of (+)-α-Naphthylphenylmethylsilane with Carbon Tetrachloride.**—In a 100-ml one-necked round-bottom

(3) L. H. Sommer, C. L. Frye, G. A. Parker, and K. W. Michael, *J. Amer. Chem. Soc.*, **86**, 3271 (1964).
(4) L. H. Sommer, K. W. Michael, and W. D. Korte, *ibid.*, **89**, 868 (1967).
(5) Unpublished work of L. H. Sommer and M. A. Silverman; see M. A. Silverman, Ph.D. Thesis, University of California at Davis, 1970.
(6) L. H. Sommer and K. T. Rosborough, *J. Amer. Chem. Soc.*, **91**, 7067 (1969).
(7) A. G. Brook and G. J. D. Peddle, *ibid.*, **85**, 2338 (1963).
(8) Y. Nagai, K. Yamazaki, I. Shiojima, N. Kobori, and M. Hayashi, *J. Organometal. Chem.*, **9**, 21 (1967).
(9) S. W. Bennett, C. Eaborn, A. Hussain, and R. A. Jackson, *ibid.*, **16**, 36 (1969).
(10) For recent esr work and pertinent recent references, see S. W. Bennett, C. Eaborn, A. Hudson, R. A. Jackson, and K. D. J. Root, *J. Chem. Soc. A*, 348 (1970).
(11) M. E. Jacox and D. E. Milligan, *J. Chem. Phys.*, **49**, 3130 (1968).
(12) D. E. Milligan and M. E. Jacox, *ibid.*, **49**, 5330 (1968).

flask equipped with a reflux condenser and a nitrogen inlet tube were placed 5.0 g (0.02 mol) of (+)-$R_3Si^*H$, $[\alpha]D$ +35.0° (*c* 4.0, pentane), and 0.6 g (0.0025 mol) of benzoyl peroxide in 40 ml of carbon tetrachloride. The solution was refluxed for 10 hr and the solvent was removed under vacuum. The remaining oil, $[\alpha]D$ −6.3° (*c* 4.0, pentane), had ir and nmr spectra identical with those of authentic $R_3SiCl$. The optical purity is 97%.

**Reaction of (+)-Phenylneopentylmethylsilane with $CCl_4$.**—In a 25-ml round-bottom flask equipped with a reflux condenser and nitrogen inlet tube were placed 1.8460 g (9.61 mmol) of $C_5H_{11}$-PhMeSiH, $[\alpha]D$ +1.56° (c 9.6, pentane), and 0.2326 g (0.961 mmol) of benzoyl peroxide in 10 ml of carbon tetrachloride. The solution was refluxed under nitrogen for 9.5 hr and then transferred quantitatively to a polarimeter tube, and a rotation was taken. Calculation yielded $[\alpha]D$ +4.59° (*c* 7.75, $CCl_4$). Ir and nmr spectra were identical with those of authentic phenylneopentylmethylchlorosilane and thus no $R_3SiH$ remained unreacted. The product was 100% optically pure from its specific rotation.

**Reaction of (+)-α-Naphthylpentafluorophenylmethylsilane with $CCl_4$.**—In a 25-ml round-bottom flask equipped with a reflux condenser and a nitrogen inlet tube were placed 0.598 g (1.77 mmol) of (+)-α-naphthylpentafluorophenylmethylsilane, $[\alpha]D$ +22.4° (*c* 1.75, $CCl_4$), and 0.05 g (0.21 mmol) of benzoyl peroxide in 3 ml of carbon tetrachloride and the solution was refluxed for 7 hr. Nmr indicated 34.1% conversion of the silane to the chlorosilane. A rotation of the mixture was taken, and calculation yielded $\phi$ = 82.8° (*c* 2.4, $CCl_4$). Calculations (see Treatment of Cyclohexane Dilution Experiments) showed that the specific rotation of the chlorosilane was $[\alpha]D$ +25.7°, which indicated an optical purity of 90%. The product was identified by nmr and glpc analyses.

**Reaction of (+)-1,2,2,2-Tetraphenyl-1-methyldisilane with $CCl_4$.**—In a 25-ml round-bottom flask equipped with a reflux condenser and a nitrogen inlet tube were placed 1.6744 g (4.40 mmol) of (+)-$Ph_3SiPhMeSi^*H$, $[\alpha]D$ +7.27° (*c* 4.0, $CCl_4$), and 0.02662 g (0.11 mmol) of benzoyl peroxide in 5 ml of carbon tetrachloride and the solution was refluxed for 0.5 hr. The solution was transferred quantitatively to a polarimeter tube. The observed rotation was 0.0°. Nmr and ir spectra were identical with those of authentic $Ph_3SiPhMeSiCl$.

**Reaction of Racemic 1,2,2,2-Tetraphenyl-1-methyldisilane and (−)-1,2,2,2-Tetraphenyl-1-methyl-1-chlorodisilane with $CCl_4$.**—The specific rotation of a solution of 1.57 g (3.8 mmol) of (−)-$Ph_3SiPhMeSi^*Cl$, 1.02 g (2.68 mmol) of (±)-$Ph_3SiPhMeSiH$, and 0.21 g (0.87 mmol) of benzoyl peroxide in 7 ml of carbon tetrachloride was $[\alpha]D$ −1.80° (*c* 12.0, $CCl_4$). The solution was refluxed under nitrogen in a 25-ml round-bottom flask for 2 hr and the contents were transferred quantitatively to a polarimeter tube for an observed rotation. Calculation yielded $[\alpha]D$ −1.74° (*c* 11, $CCl_4$). Therefore, the chlorodisilane wss optically stable under the conditions of the reaction.

**Reaction of (+)-Pentafluorophenylphenylmethylsilane with $CCl_4$.**—In a 25-ml round-bottom flask were placed 1.6 g (5.6 mmol) of $C_6F_5PhMeSi^*H$, $[\alpha]D$ +3.53°, and 0.15 g (0.62 mmol) of benzoyl peroxide in 7 ml of carbon tetrachloride and the solution was refluxed under nitrogen for 3.5 hr. The contents were transferred quantitatively to a polarimeter tube and an observed rotation was taken; calculations yielded $\phi$ = −7.06°. Nmr indicated 27.8% conversion to the chlorosilane which, therefore, calculating from the molecular rotation (see Treatment of Cyclohexane Dilution Experiments), would have a specific rotation of $[\alpha]D$ −16.0° and an optical purity of 84%. Products were confirmed by nmr and ir analyses compared to those of authentic material.

**Reaction of (+)-Benzhydrylphenylmethylsilane with $CCl_4$.**—In a 25-ml round-bottom flask were placed 0.8996 g (3.1 mmol) of benzhydrylphenylmethylsilane, $[\alpha]D$ +3.09° (c 11.0, $C_5H_{12}$), and 0.0726 g (0.31 mmol) of benzoyl peroxide in 5 ml of $CCl_4$ and the solution was refluxed for 22 hr. After removal of $CCl_4$ under vacuum, the product was purified by recrystallization from pentane, which yielded 0.5818 g of white solid which was shown by nmr to consist of 27 wt % SiH and 73 wt % SiCl. Calculation gave $[\alpha]D$ SiCl + 13.6°, and this corresponded to 100% retention of configuration.

**B. Dilution Experiments. Preparation of Neopentyllithium.**—In a 500-ml three-necked flask equipped with reflux condenser, mechanical stirrer, dropping funnel, and nitrogen inlet tube were placed 17.35 g (2.5 g-atoms) of lithium wire (pounded flat under dry pentane and cut immediately prior to reaction into the flask under a stream of nitrogen) and 300 ml of anhydrous ether (distilled from $LiAlH_4$). To this mixture was added slowly 49 g (0.46 mol) of neopentyl chloride over 2.5 hr with rapid stirring. The solution was stirred for an additional 2.5 hr and an aliquot was removed and poured into distilled water. This solution was titrated with standard acid and found to be 1.4 *N* in the organometallic.

**Reaction of (+)-α-Naphthylphenylmethylsilane and 100% $CCl_4$.**—In a 100-ml round-bottom flask equipped with a nitrogen inlet tube and a reflux condenser were placed 5.0 g (0.02 mol) of (+)-α-naphthylphenylmethylsilane, $[\alpha]D$ +35.0°, and 0.6 g (0.0025 mol) of benzoyl peroxide in 40 ml of carbon tetrachloride and the solution was refluxed under nitrogen for 10 hr. The solvent was stripped off under vacuum and the remaining viscous oil was taken up in 40 ml of anhydrous ether and cooled with an ice bath. To this solution was added rapidly 29 ml (0.04 mol) of the previously prepared neopentyllithium solution, which had been cooled by an ice bath, and the mixture was allowed to stand with occasional swirling for 20 min. The dark gray solution was then poured onto a slurry of ice, dilute HCl (5%), and pentane and the organic layer was washed three times with water. The organic layer was dried over sodium sulfate overnight and the solvent was then removed on the steam bath. The yellow oil remaining was taken up in 50 ml of pentane, adsorbed on a 19 × 50 cm silica gel column, and eluted with 300 ml of pentane followed by 500 ml of a pentane–benzene solution, 85:15 (v/v). The solvent was removed on the steam bath, leaving a clear, viscous oil, $[\alpha]D$ +21.4° (*c* 3, pentane), 5.7 g (90%). The ir spectrum was identical with that of authentic α-naphthylneopentylphenylmethylsilane.

**Reaction of (+)-α-Naphthylphenylmethylsilane, 75% Carbon Tetrachloride, and 25% Benzene.**—In a 100-ml round-bottom flask equipped with a nitrogen inlet tube and a reflux condenser were placed 5 g (0.02 mol) of (+)-$R_3Si^*H$, $[\alpha]D$ +35.0°, and 0.6 g (0.0025 mol) of benzoyl peroxide in 30 ml of carbon tetrachloride and 10 ml of benzene, and the solution was refluxed under nitrogen for 10 hr. The procedure and work-up described above for formation and isolation of the (+)-α-naphthylneopentylphenylmethylsilane yielded 5.6 g (88%) of a viscous oil, $[\alpha]D$ +20.1° (*c* 4.5, pentane). The infrared spectrum was identical with that of an authentic sample.

**Reaction of (+)-α-Naphthylphenylmethylsilane, 50% Carbon Tetrachloride, and 50% Benzene.**—In a 100-ml round-bottom flask equipped with a nitrogen inlet tube and a reflux condenser were placed 5 g (0.02 mol) of (+)-$R_3Si^*H$, $[\alpha]D$ +35.0°, and 0.6 g (0.0025 mol) of benzoyl peroxide in 20 ml of carbon tetrachloride and 20 ml of benzene and the solution was refluxed under nitrogen for 10 hr. The procedure and work-up described previously for the formation and isolation of (+)-α-naphthylneopentylphenylmethylsilane yielded 5.8 g (91%) of a clear, viscous oil, $[\alpha]D$ +18.4° (*c* 4.4, pentane). The infrared spectrum was identical with that of an authentic sample.

**Reaction of (+)-α-Naphthylphenylmethylsilane, 25% Carbon Tetrachloride, and 75% Benzene.**—In a 100-ml round-bottom flask equipped with a nitrogen inlet tube and a reflux condenser were placed 5.0 g (0.02 mol) of (+)-α-naphthylphenylmethylsilane, $[\alpha]D$ +35.0°, and 0.6 g (0.0025 mol) of benzoyl peroxide in 10 ml of carbon tetrachloride and 30 ml of benzene and the solution was refluxed under nitrogen for 10 hr. The procedure and work-up described previously for the formation and isolation of (+)-α-naphthylneopentylphenylmethylsilane yielded 5.6 g (88%) of a clear, viscous oil, $[\alpha]D$ +15.3° (*c* 4.2, pentane). The infrared spectrum was identical with that of an authentic sample.

**Reaction of (+)-α-Naphthylphenylmethylsilane, 10% Carbon Tetrachloride, and 90% Benzene.**—In a 100-ml round-bottom flask equipped with a nitrogen inlet tube and reflux condenser were placed 5.0 g (0.02 mol) of (+)-α-naphthylphenylmethylsilane, $[\alpha]D$ +35.0°, and 0.6 g (0.0025 mol) of benzoyl peroxide in 4 ml of carbon tetrachloride and 36 ml of benzene and the solution was refluxed under nitrogen for 10 hr. The procedure and work-up previously described for the formation and isolation of (+)-α-naphthylneopentylphenylmethylsilane yielded 5.4 g (85%) of a clear, viscous oil, $[\alpha]D$ +10.4° (*c* 3.2, pentane). The infrared spectrum was identical with that of an authentic sample.

**Treatment of Cyclohexane Dilution Experiments.**—In the reaction of (+)-$R_3Si^*H$ and carbon tetrachloride diluted with cyclohexane, the final solution contains both (+)-$R_3Si^*H$ and (−)-$R_3Si^*Cl$. If it is assumed that the unreacted silane has retained its original rotation (this has been shown to be correct), the rota-

tion of the chlorosilane can be calculated from the following equation

$$\frac{[\alpha]_D \text{ MW moles}}{100} + \frac{[\alpha]_D' \text{ MW' moles'}}{100} = \phi \text{ moles''}$$

where $[\alpha]_D$ = specific rotation of the remaining (+)-$R_3Si^*H$, MW = molecular weight of $R_3Si^*H$, moles = moles of $R_3Si^*H$ remaining after reaction, $[\alpha]_D'$ = specific rotation of (−)-$R_3Si^*Cl$, MW' = molecular weight of $R_3Si^*Cl$, moles' = moles of $R_3Si^*Cl$ formed in reaction, $\phi$ = molecular rotation of reaction mixture = (observed rotation) (ml)/(path length, dm) (moles'') (100), and moles'' = total moles of reactant.

Therefore, from the gross molecular rotation of the reaction mixture and an $[\alpha]_D$ of +35.0° for $R_3Si^*H$, the specific rotation of the formed (−)-$R_3Si^*Cl$ can be calculated. The amount of silane remaining (moles) and the amount of chlorosilane formed (moles') can be obtained from glpc or nmr analysis.

**Reaction of (+)-α-Naphthylphenylmethylsilane and $CCl_4$.**—In a 25-ml round-bottom flask equipped with a reflux condenser and a nitrogen inlet tube were placed 2.0 g (0.008 mol) of (+)-α-naphthylphenylmethylsilane, $[\alpha]_D$ +35.0°, and 0.19 g (0.0008 mol) of benzoyl peroxide in 8 ml of carbon tetrachloride. The resulting solution was refluxed for 14 hr under nitrogen. The reaction mixture was transferred quantitatively to a polarimeter tube and a rotation was taken. Calculations yielded $\phi$ = −6.60° (c 6.6, $CCl_4$). The solvent was removed, the remaining oil was taken up in cyclohexane, and a known quantity of phenanthrene was added [TCF = phenanthrene/$R_3SiH$ = 1.05 (weight basis), phenanthrene/$R_3SiCl$ = 1.42, $R_3SiH/R_3SiCl$ = 1.34]. The solution was analyzed by glpc and 0.18 g of $R_3Si^*H$ and 2.1 g of $R_3Si^*Cl$ were found to be present. Calculation using the equation previously described yielded $[\alpha]_D$ −5.5° for the chlorosilane produced. Nmr, ir, and glpc analyses were consistent with the assigned structures.

**Reaction of (+)-α-Naphthylphenylmethylsilane with 50% Carbon Tetrachloride and 50% Cyclohexane.**—In a 25-ml round-bottom flask equipped with a reflux condenser and a nitrogen inlet tube were placed 2.0 g (0.008 mol) of (+)-$R_3Si^*H$, $[\alpha]_D$ +35.0°, and 0.19 g (0.0008 mol) of benzoyl peroxide in 4 ml of carbon tetrachloride and 4 ml of cyclohexane. The solution was refluxed for 14 hr under nitrogen. Following the procedure described above yielded $\phi$ = −1.34° (c 6.6, $CCl_4$) for the molecular rotation of the reaction mixture and $[\alpha]_D$ −3.84 for the $R_3Si^*Cl$ formed (0.21 g of $R_3Si^*H$ remaining and 2.0 g of $R_3Si^*Cl$ formed).

**Reaction of (+)-α-Naphthylphenylmethylsilane with 33% Carbon Tetrachloride and 67% Cyclohexane.**—In a 25-ml round-bottom flask equipped with a reflux condenser and a nitrogen inlet tube were placed 2.0 g (0.008 mol) of (+)-$R_3Si^*H$, $[\alpha]_D$ +35.0°, 0.19 g (0.0008 mol) of benzoyl peroxide in 2.6 ml of carbon tetrachloride, and 5.4 ml of cyclohexane, and the solution was refluxed for 14 hr under nitrogen. The procedure described previously yielded $\phi$ = +17.2° (c 6.6, $CCl_4$) for the molecular rotation of the reaction mixture and $[\alpha]_D$ −2.78° for the $R_3Si^*Cl$ formed (0.54 g of $R_3Si^*H$ remaining and 1.8 g of $R_3Si^*Cl$ formed).

**Reaction of α-Naphthylphenylmethyldeuteriosilane and Carbon Tetrachloride.**—In a 25-ml round-bottom flask were placed 1.1000 g (4.42 mmol) of $R_3SiD$ and 0.1000 g (0.414 mmol) of benzoyl peroxide in 5 ml of carbon tetrachloride. The solution was refluxed for 11 hr under nitrogen. The volatile material was removed under vacuum and trapped in a flask cooled by a Dry Ice–acetone bath. The chloroform formed was isolated by preparative glpc and a mass spectrum was taken. The results indicated that 98% of the hydrogen in the chloroform was deuterium.

**Reaction of α-Naphthylphenylmethyldeuteriosilane and Cyclohexane.**—In a 25-ml round-bottom flask were placed 0.3000 g (1.2 mmol) of α-naphthylphenylmethyldeuteriosilane and 0.0300 g (0.124 mmol) of benzoyl peroxide in 4 ml of cyclohexane and the solution was refluxed for 17 hr under nitrogen. Infrared examination of the reaction mixture indicated that no $R_3SiH$ formed.

**Reaction of α-Naphthylphenylmethyldeuteriosilane, Chloroform, Toluene, Benzene, and 1,3,5-Trimethylbenzene.**—In a manner analogous to that described above, $R_3SiD$ and benzoyl peroxide were treated with $CHCl_3$, PhMe, PhH, and $PhMe_3$. Infrared analysis indicated that no $R_3SiH$ formed in any of the reactions.

**Registry No.**—**1**, 1025-08-7; **1**-Cl, 960-82-7; **2**, 1770-59-8; **2**-Cl, 15942-84-4; **3**, 36358-49-3; **3**-Cl, 36358-50-6; **4**, 36411-23-1; **4**-Cl, 36358-51-7; **5**, 15726-86-0; **5**-Cl, 15942-85-5; carbon tetrachloride, 56-23-5.

**Acknowledgment.**—Support of this work by the National Science Foundation is gratefully acknowledged.

# Stereochemistry of Addition Reactions of Allenes. VI. Orientation and Stereochemistry of Radical Addition

LARRY R. BYRD AND MARJORIE C. CASERIO*[1,2]

*Department of Chemistry, University of California, Irvine, California 92664*

*Received July 5, 1972*

Products of radical addition of *p*-toluenesulfonyl iodide, $ArSO_2I$, to various allenes (propadiene, 1,2-butadiene, 3-methyl-1,2-butadiene, 2,3-pentadiene, 2-methyl-2,3-pentadiene, and 1,2-cyclononadiene) have been identified. Each allene except propadiene gave an allylic iodide by way of central attack on the allenic system by arylsulfonyl radicals. Evidence supporting the intervention of symmetrical allylic radicals was obtained from a study of the addition of $ArSO_2I$ to optically active 2,3-pentadiene and 1,2-cyclononadiene. Radical addition of halomethanes, $CF_3I$, $CH_3I$, and $CCl_3Br$, to 2,3-pentadiene gave products of terminal attack by $CX_3$ radicals (X = F, H, Cl) accompanied by 41–49% central attack in the case of $CCl_3Br$. The stereospecificity of addition of $BrCCl_3$ to (+)-2,3-pentadiene was found to be almost negligible, indicating that the products are formed from symmetrical allylic radicals and configurationally unstable vinylic radicals. The factors that influence the orientation of radical addition to allenes are discussed.

Radical-chain additions to allenes are presumed to involve radical intermediates of allylic structure by way of initial attack at the central allenic carbon, and of vinylic structure by attack at the terminal carbons. The degree to which radicals of either structure are involved depends on the structure of the starting allene, the nature of the attacking radicals, and the reaction conditions.[3] Nevertheless, orientation data for the addition of various radical reagents to propadiene do not reveal any obvious correlation between the nature of the attacking radical and its regioselectivity. For example, under kinetic control, where reversibility

(1) The authors gratefully acknowledge the support received from the donors of the Petroleum Research Fund of the American Chemical Society (PRF 2357-A1, 4).

(2) Part V: L. R. Byrd and M. C. Caserio, *J. Amer. Chem. Soc.*, **93**, 5758 (1971).

(3) (a) M. C. Caserio in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 239. (b) For a thoughtful review on structure and reactivity in free-radical chemistry, see C. Ruchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).

TABLE I

SELECTIVITY IN RADICAL ADDITIONS TO PROPADIENE AND 2,3-PENTADIENE

| | | $CH_2=C=CH_2$ | | | $CH_3CH=C=CHCH_3$ | | |
|---|---|---|---|---|---|---|---|
| Reagent | Attacking radical | Terminal attack[a] | Central attack[a] | Ref | Terminal attack[a] | Central attack[a] | Ref |
| HBr[b] | Br· | | 100 | 9 | 6 | 94 | 6 |
| HBr[c] | Br· | 66 | 33 | 4 | | | |
| $SF_6$[d] | $^{18}F$ | ~50 | ~50 | 8 | | | |
| $N_2F_4$ | F· | | 100 | 10 | | | |
| $PH_3$ | $H_2P$· | | 100 | 11 | | | |
| $(CH_3)_3SnH$ | $(CH_3)_3Sn$· | 55 | 45 | 5 | | 100 | 5 |
| $C_6H_5SH$ | $C_6H_5S$· | 75 | 25 | 6 | | | |
| $p$-$CH_3C_6H_4SO_2I$ | $p$-$CH_3C_6H_4SO_2$· | 100 | | 12 | | 100 | *e* |
| $(CH_3)_3COCl$ | $(CH_3)_3CO$· | | | | | 100 | 17 |
| $CF_3I$ | $F_3C$· | 100 | | 7 | 100 | | *e* |
| $CCl_3Br$ | $Cl_3C$· | 100 | | 6 | 59 | 41 | *e* |
| $CH_3I$ | $H_3C$· | 100 | | 7 | 100 | | *e* |

[a] Per cent distribution, statistical correction not included. [b] Gas phase. [c] Liquid phase under conditions of kinetic control. [d] Gas-phase reaction of $^{18}F$ from $^{19}F(n,2n)$ in excess $SF_6$. Moderated by $SF_6$ at $\tau$ 3500, the intermediate radicals were scavenged by HI. [e] Present work.

of initial attack is not a factor, fluorine atoms, bromine atoms (in the liquid phase),[4] trimethyltin,[5] and benzenethiyl radicals[6] are relatively nonselective (*cf.* Table I[4-12]). In contrast, radicals of the type $CX_3$· are highly selective and attack the terminal carbons exclusively, regardless of the nature of X (F, Cl, or H).[6-8]

Studies of radical additions to substituted allenes are more limited, but the results of HBr,[9] thiol,[13] and trimethyltin hydride[6] additions to methylated allenes indicate a strong preference for central radical attack with increasing methyl substitution. The origin of this effect is not entirely clear, although it must certainly be related to the steric and electronic influence of methyl substituents on the reactivity of the central over the terminal positions provided that attack at either site is irreversible. Of special interest, however, is the question of whether the reactivity of the central carbon is enhanced by formation of resonance-stabilized allylic intermediates or whether these intermediates are actually nonplanar localized radicals. To investigate this question, we have chosen to study radical addition to optically active allenes using reagents that can in principle lead to asymmetric adducts. Induction of activity in the products would provide evidence for the intervention of dissymmetric radicals, whereas formation of racemic adducts would suggest that products were formed from planar delocalized allyl radicals. The allenes chosen for this work were 2,3-pentadiene and 1,2-cyclononadiene, both of which are readily available and easily resolved. Unfortunately, a study of the addition of HBr, thiols, and tin hydrides to these allenes is unsuited to our objectives since the adducts are achiral. We therefore studied the radical addition of *p*-toluenesulfonyl iodide (tosyl iodide) and, since little information was available on the orientation of addition of this reagent, we extended the study to include symmetrical allenes. We have also investigated the radical additions of $CF_3I$, $CCl_3Br$, and $CH_3I$ to 2,3-pentadiene and related allenes, the results of which are pertinent to the overall question of orientation.

## Results

**Addition of Tosyl Iodide.**—The allenes studied included propadiene, 1,2-butadiene, 3-methyl-1,2-butadiene, 2,3-pentadiene, 2-methyl-2,3-pentadiene, and 1,2-cyclononadiene. A twofold molar excess of allenic hydrocarbon to freshly prepared tosyl iodide in ether or pentane was irradiated in a sealed, thick-walled Pyrex cylinder with a 200-W heat lamp until reaction was complete, which typically required 20 min. Comparable reaction mixtures maintained in the dark were unreactive over a period of at least 6 hr with the exception of 1,2-cyclononadiene, which underwent spontaneous reaction as low as 0°. The monoadducts formed were isolated as crystalline solids in nearly quantitative yields. Apart from the *tert*-allylic iodide **6** obtained from 2-methyl-2,3-pentadiene, the adducts were stable to the reaction conditions; however, isolation of **6** within minutes of reaction was necessary to prevent its resinification. The structure of each adduct was established from its nmr spectrum (Table II) and from the structure of the products obtained on solvolysis of the adduct in methanolic silver tetrafluoroborate (Table III). The tosyl iodide reactions were remarkably straightforward and selective in that only one crystalline monoadduct was obtained from each allene. Consistent with the previously reported results of Truce and Wolf,[12] propadiene was the only allene that produced a vinylic iodide **1** (eq 1) and

$$CH_2=C=CH_2 \xrightarrow[h\nu]{ArSO_2I} CH_2=C(I)CH_2SO_2Ar \qquad (1)$$

a minor by-product identified as the disulfone **2**. As expected, **1** was unreactive toward methanolic silver tetrafluoroborate.

(4) (a) E. I. Heiba and W. O. Haag, *J. Org. Chem.*, **31**, 3814 (1966); D. Kovachic and L. C. Leitch, *Can. J. Chem.*, **39**, 363 (1961); K. Griesbaum, A. A. Oswald, and D. N. Hall, *J. Org. Chem.*, **29**, 2404 (1964).

(5) H. G. Kuivila, W. Rahman, and R. W. Fish, *J. Amer. Chem. Soc.*, **87**, 2835 (1965).

(6) (a) E. I. Heiba, *J. Org. Chem.*, **31**, 776 (1966); K. Griesbaum, A. A. Oswald, E. R. Quiram, and W. Naegele, *ibid.*, **28**, 1952 (1963); H. J. vander Ploeg, J. Knotnerus, and A. F. Bickel, *Recl. Trav. Chim. Pays-Bas*, **81**, 775 (1962).

(7) H. G. Meunier and P. I. Abell, *J. Phys. Chem.*, **71**, 1430 (1967); R. N. Haszeldine, K. Leedham, and B. R. Steele, *J. Chem. Soc.*, 2040 (1954).

(8) R. L. Williams and F. S. Rowland, private communication.

(9) (a) P. I. Abell and R. S. Anderson, *Tetrahedron Lett.*, 3727 (1964); (b) R. Y. Tien and P. I. Abell, *J. Org. Chem.*, **35**, 956 (1970).

(10) C. L. Bumgardner and K. G. McDaniel, *J. Amer. Chem. Soc.*, **91**, 1032 (1969).

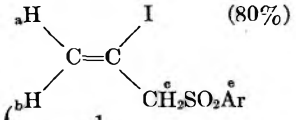
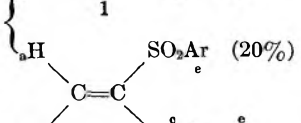
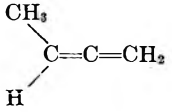
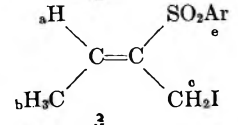
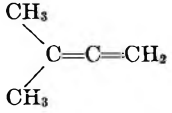
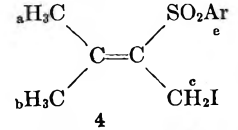
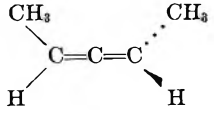
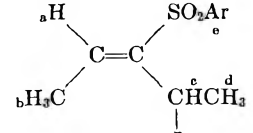
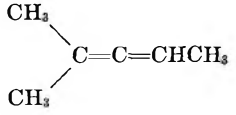
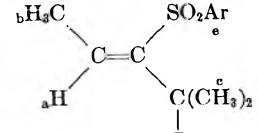
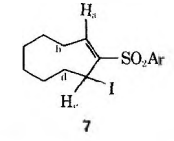
(11) H. Goldwhite, *J. Chem. Soc.*, 3901 (1965).

(12) W. E. Truce and G. C. Wolf, *Chem. Commun.*, 150 (1969).

(13) T. L. Jacobs and G. E. Illingworth, Jr., *J. Org. Chem.*, **28**, 2692 (1963).

TABLE II

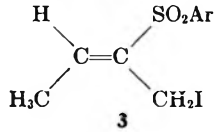
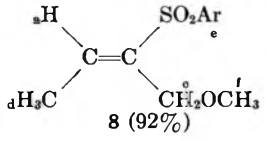
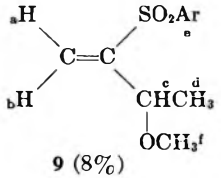
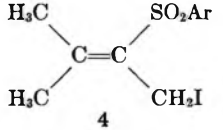
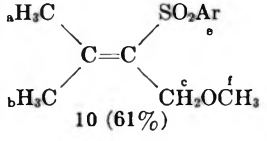
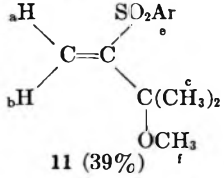
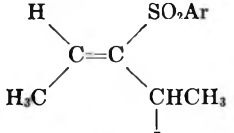
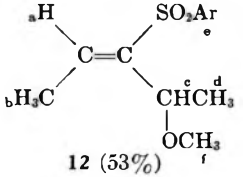
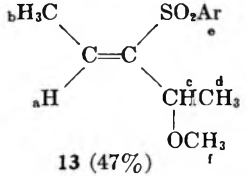
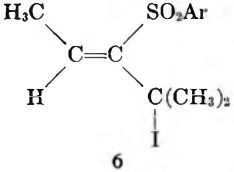
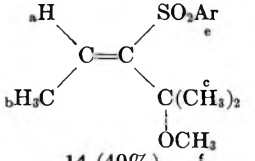
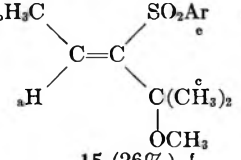
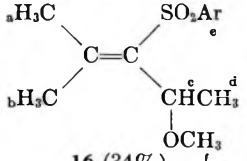
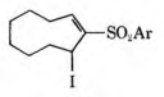
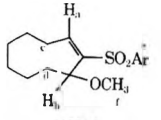
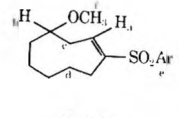
PRODUCT DISTRIBUTION IN ADDITION OF TOSYL IODIDE TO ALLENES. NMR SPECTRAL PARAMETERS OF ADDUCTS[a-c]

| Allene | Compd | Mp, °C[d] | Yield, % | $\delta_a$ | $\delta_b$ | $\delta_c$ | $\delta_d$ | $\delta_e$ | $J$, Hz |
|---|---|---|---|---|---|---|---|---|---|
| $CH_2=C=CH_2$ |  (80%) | 74–76 | | 6.12 (m) | 5.91 (d) | 4.08 (d) | | 7.05–7.75 (m) | ab = 1.9<br>ac = 0.9 |
| | 1 | | 64[e] | | | | | | |
| |  (20%) | 152–153 | | 6.48 (d) | 6.33 (m) | 3.95 (d) | | 7.0–7.6 (m) | ab = 1.1<br>bc = 1.0 |
| | 2 | | | | | | | | |
|  |  | 104–106 | 73[e] | 7.12 (q) | 1.74 (d) | 3.97 (s) | | 7.1–7.9 (m) | ab = 7.1 |
| | 3 | | | | | | | | |
|  |  | 77–80 | 73[e] | 2.02 (s) | 1.84 (s) | 4.33 (s) | | 7.1–8.0 (m) | |
| | 4 | | | | | | | | |
|  |  | 110–112 dec | 82[e] | 7.14 (q) | 1.90 (d) | 4.98 (q) | 1.87 (d) | 7.2–7.8 (m) | ab = 7.5<br>cd = 7.4<br>ac = 0.5 |
| | 5 | | | | | | | | |
|  |  | *f* | 99[f] | 5.78 (q) | 2.03 (d) | 2.01 (d) | | 7.2–7.8 (m) | ab = 7.5<br>ac = 1.8 |
| | 6 | | | | | | | | |
|  |  | 104–106 dec | 80[e] | 7.15 (dd) | 2.0–3.2 (m) | 5.0 (dd) | 1.8 (m) | 7.2–7.9 (m) | ab = 11, 5<br>ac = 1.3<br>cd = 11, 5 |
| | 7 | | | | | | | | |

[a] Ar = $C_6H_4$-*p*-$CH_3$. [b] Chemical shifts are reported in parts per million downfield from internal TMS; spectra were recorded as 25% solutions in $CDCl_3$. [c] $\delta_e$ refers to phenyl protons; $\delta_{p\text{-}CH_3}$ = 2.43 for all adducts. [d] Melting points were taken after one recrystallization from 95% ethanol. [e] Crude yield, prior to recrystallization, was practically quantitative. [f] This figure represents a crude yield; the adduct decomposed before the melting point could be determined.

TABLE III

PRODUCT DISTRIBUTION IN SILVER-ASSISTED METHANOLYSIS OF ALLENE–TOSYL IODIDE ADDUCTS. NMR SPECTRAL PARAMETERS OF PRODUCTS[a,b]

| Adduct | Methanolysis products | No. | $\delta_a$ | $\delta_b$ | $\delta_c$ | $\delta_d$ | $\delta_e$ | $\delta_f$ | $J$, Hz |
|---|---|---|---|---|---|---|---|---|---|
|  3 |  8 (92%) | 8 | 7.15 (q) | 1.88 (d) | 4.14 (s) | | 7.1–7.9 (m) | 2.98 (s) | ab = 7.1 |
| |  9 (8%) | 9 | 6.37 (s) | 5.97 (s) | 3.51 (q) | 2.32 (d) | 7.1–7.9 (m) | 2.86 (s) | cd = 6.5 |
|  4 |  10 (61%) | 10 | 2.07 (s) | 1.91 (s) | 4.26 (s) | | 7.1–7.9 (m) | 3.21 (s) | |
| |  11 (39%) | 11 | 6.38 (s) | 6.02 (s) | 1.38 (s) | | 7.1–7.9 (m) | 2.75 (s) | ab = 0 |
|  5 |  12 (53%) | 12 | 7.10 (q) | 1.90 (d) | 4.12 (q) | 1.29 (d) | 7.2–7.8 (m) | 2.78 (s) | ab = 7.4<br>ac = 0.7<br>cd = 6.4 |
| |  13 (47%) | 13 | 6.43 (q) | 2.15 (d) | 4.12 (q) | 1.29 (d) | 7.2–7.8 (m) | 2.92 (s) | ab = 7.4<br>ac = 0.7<br>cd = 6.4<br>bc = 0.7 |
|  6 |  14 (40%) | 14 | 7.27 (q) | 2.31 (d) | 1.48 or 1.36(s) | | 7.1–7.9 (m) | 2.95 (s) | ab = 7.6 |
| |  15 (26%) | 15 | 2.38 or 2.08 (s) | 2.08 or 2.38 (s) | 4.48 (q) | 1.38 (d) | 7.1–7.9 (m) | 2.93 (s) | cd = 6.7 |
| |  16 (34%) | 16 | 6.67 (q) | 2.12 (d) | 1.36 or 1.48 (s) | | 7.1–7.9 (m) | 2.97 (s) | ab = 7.8 |
|  7 |  17 (72%) | 17 | 7.18 (dd) | 4.25 (m) | 2.0–2.5 (m) | 1.1–2.0 (m) | 7.2–7.9 (m) | 2.86 (s) | ac = 7, 12 |
| |  18 (28%) | 18 | 7.12 (dd) | 2.6–3.2 | 2.0–3.3 (m) | 1.1–2.2 (m) | 7.2–7.9 (m) | 3.23 (s) | ac = 7, 12 |

[a] Ar = $C_6H_4$-$p$-$CH_3$. [b] Chemical shifts are reported from internal TMS; spectra were recorded as 25% solutions in $CDCl_3$; $\delta_e$ refers to phenyl protons; $\delta_{p\text{-}CH_3}$ = 2.42 for all products.

In contrast, the substituted allenes gave only allylic iodides **3–7** (Table II). Solvolysis of these adducts occurred readily in methanolic silver tetrafluoroborate and was accompanied by allylic rearrangement, geometric isomerization, and, in the case of 1,2-cyclononadiene, transannular hydride shifts. The structure and nmr spectral parameters of the solvolysis products **8–18** are summarized in Table III. Whereas 2,3-pentadiene has been reported to react with tosyl iodide to give an adduct of the opposite orientation to that reported here,[13] the spectral parameters and chemical behavior of **5** leave no doubt that the adduct we obtained from 2,3-pentadiene is 4-iodo-3-tosyl-2-pentene (**5**).

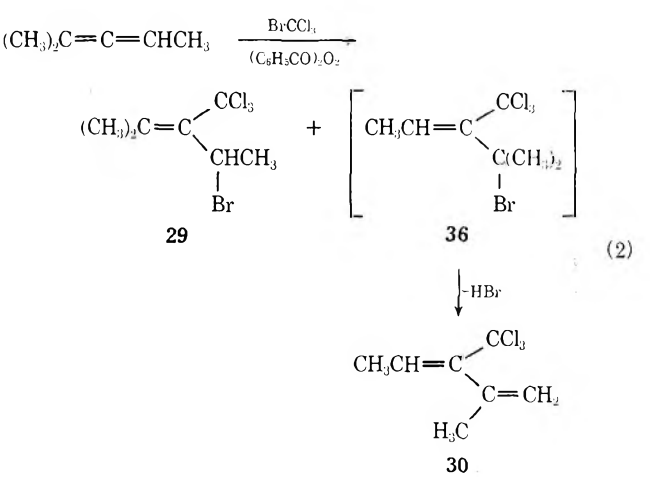
Addition of tosyl iodide to partially resolved (*S*)-(+)-2,3-pentadiene having a specific rotation of $[\alpha]^{28}D$ 23.20 ± 0.05° (*c* 30, ether) gave *cis*-4-iodo-3-tosyl-2-pentene (**5**), which showed *no observable activity* either before or after purification by recrystallization. The recovered unreacted 2,3-pentadiene showed only a small loss in initial optical activity, $[\alpha]^{28}D$ 21.61 ± 0.05° (*c* 27, ether). Addition of tosyl iodide to partially resolved (*S*)-(−)-1,2-cyclononadiene with $[\alpha]^{28}D$ −23.30 + 0.05° (neat) gave *cis*-3-iodo-2-tosylcyclononene (**7**), which like adduct **5** from (+)-2,3-pentadiene, had no measurable activity. However, the recovered unreacted 1,2-cyclononadiene had, after distillation, lost most of its observed rotation and in fact showed a slight positive rotation, $[\alpha]^{28}D$ 0.46 ± 0.05° (neat).

**Addition of Iodomethane.**—Reaction mixtures comprised of a twofold excess of $CH_3I$ to allene (2,3-pentadiene or 2-methyl-2,3-pentadiene) were irradiated in sealed, degassed quartz test tubes using a low-pressure mercury vapor lamp as the light source. Typically, 12 hr of irradiation brought about a 45% conversion of the allene to a complex mixture of products of which some 23% consisted of 1:1 adducts; these were isolated from the crude reaction mixtures by flash distillation followed by preparative glpc. Their structures were established by nmr and infrared spectroscopy and from the fact that they were *inert* to methanolic $AgBF_4$. The pertinent structural data are summarized in Table IV, from which it may be noted that the only isolable 1:1 adducts of iodomethane addition to 2,3-pentadiene and 2-methyl-2,3-pentadiene are vinylic iodides, **19–22**. This result, however, does not exclude the possibility that allylic iodides may be formed, since they would be expected photolyze under the reaction conditions. Attempts to analyze the complex mixture of higher molecular weight products were unsuccessful and we can comment only that their spectral properties (nmr, ir) are incompatible with diadducts or telomers derived in any simple fashion from monoadducts of either orientation.

**Addition of Iodotrifluoromethane to 2,3-Pentadiene.**—A twofold molar excess of $CF_3I$ was condensed in 2,3-pentadiene; the mixture was degassed and sealed in a thick-walled Pyrex tube and irradiated for 24 hr using a medium-pressure mercury vapor uv lamp. About 60% of the allene was consumed to produce a complex mixture of products of which some 44% corresponded to monoadducts. Isolation of three compounds from the monoadduct fraction was achieved by preparative glpc. Structure was assigned on the basis of $^1H$ and $^{19}F$ nmr spectra (Table IV), infrared spectra, and lack of reactivity toward methanolic $AgBF_4$. Thus, the monoadduct fraction consisted of 9.4% *trans*-3-iodo-2-pentene (**23**), 70.3% *trans*-3-iodo-4-trifluoromethyl-2-pentene (**24**), and 20.3% *cis*-3-iodo-4-trifluoromethyl-2-pentene (**25**). Formation of the minor product **23** presumably occurs by attack of iodine atoms followed by hydrogen abstraction. The major products are $CF_3I$ adducts with iodine at the vinylic position. As with methyl iodide addition, the absence of allylic iodides does not necessarily exclude their formation, since they may not be photostable. Unfortunately, the secondary products of higher molecular weight were not identified owing to the complexity of the mixture.

**Addition of Bromotrichloromethane.**—2,3-Pentadiene, 2-methyl-2,3-pentadiene, and 1,2-cyclononadiene reacted cleanly and in high yield (~70%) with bromotrichloromethane at reflux temperatures using benzoyl peroxide as the initiator. Reaction was generally complete within 2 hr. The adducts were isolated by distillation and characterized by their nmr, mass, and ir spectra and their reactivity toward $AgBF_4$ (Tables IV and V). 2,3-Pentadiene gave a mixture of 59% vinylic bromides **26** and **27** and 41% allylic bromide **28**. Using partially resolved (*S*)-(+)-2,3-pentadiene having $[\alpha]^{25}D$ 23.42 ± 0.05° (*c* 38, ether), a mixture of 51% **26** and **27** and 49% **28** was isolated which showed a low specific rotation of $[\alpha]^{24}D$ −0.33 ± 0.05 (neat). Significantly, the recovered unreacted allene had lost essentially *none* of its optical activity, $[\alpha]^{24}D$ 23.3 ± 0.1° (*c* 26, ether).

Addition of $BrCCl_3$ to 1,2-cyclononadiene gave a single monoadduct, identified as *cis*-3-bromo-2-trichloromethylcyclononene (**31**). Addition to 2-methyl-2,3-pentadiene gave the allylic bromide **29** and the diene **30**. The latter possibly forms by way of the alyllic precursor **36** by loss of HBr (eq 2).




Solvolysis of allylic bromides from the addition of $BrCCl_3$ to the three allenes studied gave a complex mixture of products from the adduct of 1,2-cyclononadiene, a mixture of *dl* and meso diethers **32** and **33** from the adduct of 2,3-pentadiene **28**, and an allylic ether **34** and diene **35** from the adduct of 2-methyl-2,3-pentadiene (Table V). Solvolysis of **28** evidently occurs at both the bromoallylic and chloroallylic sites

TABLE IV

PRODUCT DISTRIBUTION IN ADDITION OF $CX_3Y$ TO ALLENES. NMR SPECTRAL PARAMETERS OF ADDUCTS

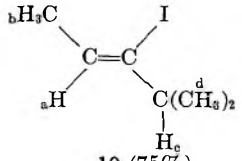
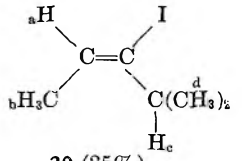
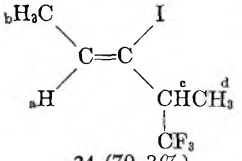
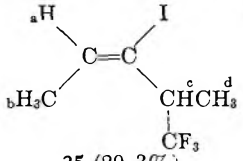
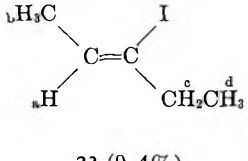
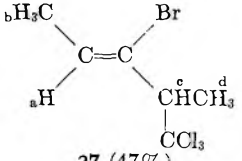
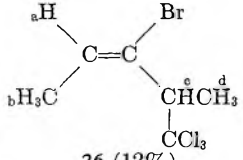
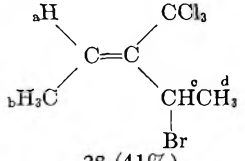
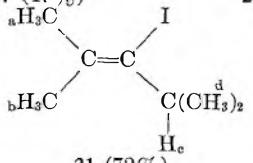
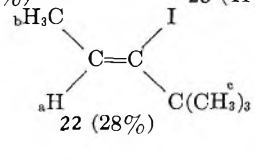
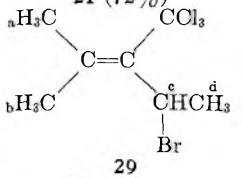
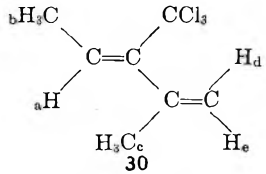
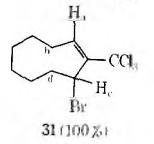
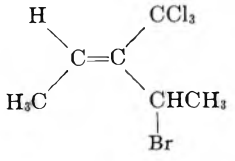
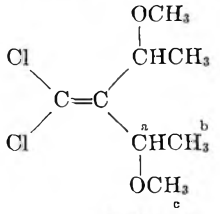
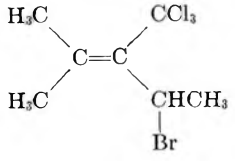
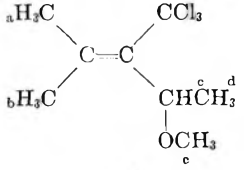
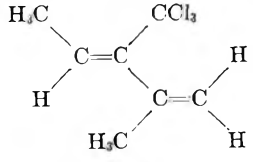
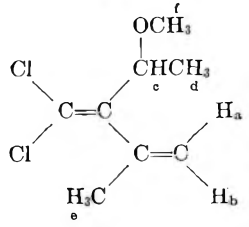
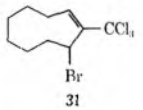
| Allene | Adding reagent | Products | No. | $\delta_a$ | $\delta_b$ | $\delta_c$ | $\delta_d$ | $\delta_e$ | $J$, Hz |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3CH{=}C{=}CHCH_3$ | $CH_3I$ |  19 (75%) | 19 | 5.66 (q) | 1.70 (d) | 1.8–2.6 (m) | 1.03 (d) | | ab = 6.6<br>cd = 6.6<br>ac = 0.9<br>bc = 0.4 |
| | |  20 (25%) | 20 | 6.17 (q) | 1.66 (d) | 1.8–2.6 (m) | 1.03 (d) | | ab = 7.4<br>cd = 6.6<br>ac = 0.4 |
| | $CF_3I$ |  24 (70.3%) | 24 | 6.01 (q) | 1.80 (d) | 3.05 (d) | 1.30 (d) | | ab = 6.4<br>cd = 7.0<br>ce = 8.8 |
| | |  25 (20.3%) | 25 | 6.70 (q) | 1.74 (d) | 3.15 (m) | 1.26 (d) | | ab = 7.3<br>cd = 7.0<br>ce = 8.8 |
| | |  23 (9.4%) | 23 | 5.59 (q) | 1.73 (d) | 2.50 (q) | 1.08 (t) | | ac = 1.3<br>ab = 6.4<br>bc = 1.3 |
| | $BrCCl_3$ |  27 (47%) | 27 | 6.18 (q) | 1.79(d) | 3.50 (q) | 1.56 (d) | | ab = 6.7<br>ac = 0.5<br>cd = 6.8 |
| | |  26 (12%) | 26 | 6.27 (q) | 1.77 (d) | 3.77 (q) | 1.52 (s) | | ab = 7.5<br>cd = 6.6 |
| | |  28 (41%) | 28 | 6.65 (q) | 1.98 (d) | 5.07 (q) | 2.07 (d) | | ab = 7.6<br>ac = 2.0<br>cd = 7.4 |
| $H_3C$<br>$C{=}C{=}CHCH_3$<br>$H_3C$ | $CH_3I$ |  21 (72%) | 21 | 1.86 or 1.92(s) | 1.92 or 1.86(s) | 2.37 (m) | 0.93 (d) | | cd = 6.5 |
| | |  22 (28%) | 22 | 5.60 (q) | 1.75 (d) | 1.18 (s) | | | ab = 6.5 |
| | $BrCCl_3$ |  29 | 29 | 1.90 or 1.92 (a) | 1.92 or 1.90 (s) | 4.80 (q) | 1.75 (d) | | cd = 6.8 |
| | |  30 | 30 | 4.98 (q) | 1.75 (d) | 3.37 (s) | 5.72 or 5.88 (s) | 5.88 or 5.72 (s) | ab = 6.8<br>ec = de = 1.0 |
|  | $BrCCl_3$ |  31 (100%) | 31 | 6.70 (dd) | 2.0–3.3 (m) | 5.02 (dd) | 1.1–2.0 (m) | | ab = 7, 12<br>cd = 6, 11<br>ac = 2.0 |

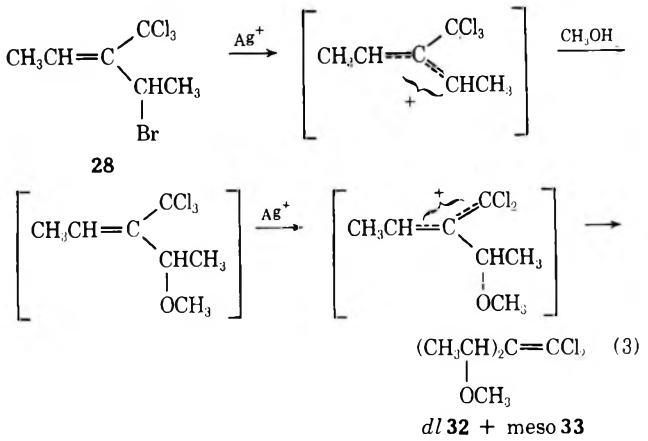
TABLE V

STRUCTURE AND SPECTRAL PARAMETERS OF METHANOLYSIS PRODUCTS OF ALLENE–$CX_3Y$ ADDUCTS[a]

| Adduct | Methanolysis product | $\delta_a$ | $\delta_b$ | $\delta_c$ | $\delta_d$ | $\delta_e$ | $\delta_f$ | $J$, Hz |
|---|---|---|---|---|---|---|---|---|
|  28 |  **32** (50%) *dl*<br>**33** (50%) meso | 4.22 or 4.30 (q) | 1.32 or 1.28 (d) | 3.18 or 3.22 (s) | | | | ab = 6.7 or 6.9 |
|  **29** |  **34** | 1.91 or 1.93 (s) | 1.93 or 1.91 (s) | 3.97 (q) | 1.16 (d) | 3.20 (s) | | cd = 6.4 |
|  **30** |  **35** | 5.40 or 5.55 (s) | 5.55 or 5.40 (s) | 4.12 (q) | 1.16 (d) | 3.37 (d) | 3.20 (s) | cd = 6.4 |
|  **31** | Complex mixture | | | | | | | |

[a] Chemical shifts are reported in parts per million downfield from internal TMS; spectra were recorded as 25% solutions in $CDCl_3$.

(eq 3). Likewise, solvolysis of the diene occurs at the trichloromethyl group.

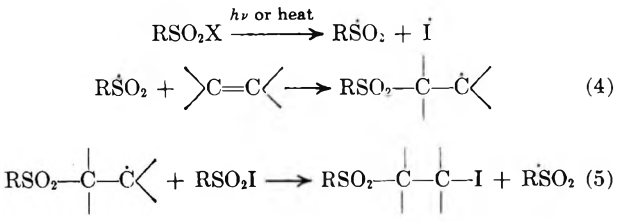


28

*dl* **32** + meso **33**

## Discussion

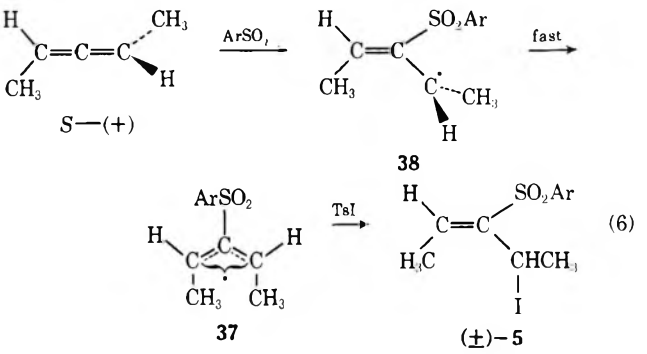
**Addition of Tosyl Iodide.**—The addition of sulfonyl halides $RSO_2X$ to alkenes is considered to be a radical-chain process in which a sulfonyl radical $RSO_2$ is the chain-carrying agent.[14,15] The propagation steps for X = I are shown in eq 4 and 5. The observed orienta-



(4)

(5)

tion of tosyl iodide addition to allenes (Table II) demonstrates the selectivity of tosyl radicals for transfer to the *terminal* positions of propadiene and to the *central* position of all the methyl analogs, including 1,2-cyclononadiene.[16] Allylic radicals are therefore implicated as intermediates in additions to methylallenes, and the question arises as to whether these radicals are nonplanar localized radicals or planar delocalized radicals. The results of addition to (*S*)-(+)-2,3-pentadiene are important in this respect. The observed formation of *racemic* adduct **5** from (+)-2,3-pentadiene and the recovery of unreacted allene of essentially retained optical purity implies that tosyl radicals attack the central carbon of 2,3-pentadiene *irreversibly* to give planar allylic intermediates **37**. If bridged or localized radicals **38** are initially formed, they must necessarily lose their dissymmetry by a 90° bond rotation to give **37** faster than they can abstract iodine atoms from tosyl iodide (eq 6). This result parallels our earlier finding that *tert*-butoxy radicals and possibly chlorine atoms attack the central carbon of 2,3-pentadiene irreversibly to give allylic intermediates which lead to racemic adducts.[17] Irreversibility of radical addition to the central carbon is also consistent with the kinetic schemes deduced for HBr[4,9] and thiol[6a] additions to allenes. It has

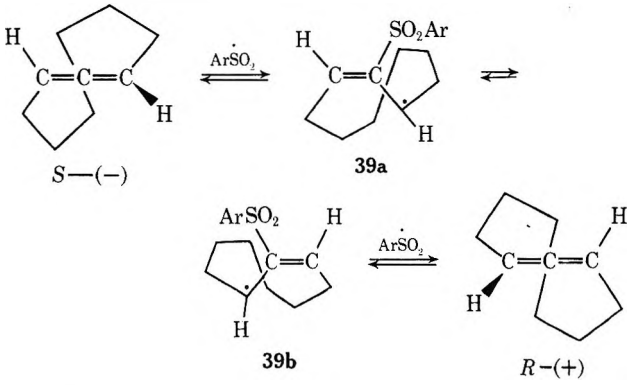


(6)

been shown for HBr additions that the hydrogen-abstraction step is rate determining.[9]

Terminal attack by tosyl radicals cannot be significant for 2,3-pentadiene, since products of this orientation were not observed and a rapid reversible attack is improbable for the reason that racemization of the allene during reaction is negligible. In contrast, a small amount of reversible terminal addition of bromine atoms to 2,3-pentadiene has been noted.[9]

Addition of tosyl iodide to (*S*)-(−)-1,2-cyclononadiene is interesting in several respects. The reaction is spontaneously initiated and both the recovered unreacted allene and the monoadduct **7** are essentially racemic. Racemization of the allene may mean that central attack by tosyl radicals is reversible in this case. Molecular models suggest that a coplanar allylic system within a nine-membered carbocycle may be less comfortable than a nonplanar system owing to torsional strain and unfavorable nonbonded interactions. A nonplanar chiral radical **39** lacks the 10 kcal of allylic resonance stabilization[18] and could conceivably be formed reversibly in a nearly thermoneutral process. Furthermore, rapid conformational interconversion of **39a** with its mirror image **39b** would lead to the recovery of a racemic adduct and racemic allene, as observed.



The behavior of 1,2-cyclononadiene in radical additions is also interesting when compared with polar additions. A major product in the ionic addition of bromine to 1,2-cyclononadiene is 1,4-dibromocyclononene arising by way of a 1,5-transannular hydride shift.[2] However, no products related to 1,5-transannular hydrogen-atom transfers were observed in the radical addition of either tosyl iodide or bromotrichloromethane to 1,2-cyclononadiene. Evidently, internal hydrogen abstraction in **39** cannot compete effectively with abstraction of a halogen atom (Br or I) from an external reagent.

(14) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 4962 (1964); S. J. Cristol and D. I. Davis, *J. Org. Chem.*, **29**, 1282 (1964).

(15) W. E. Truce and G. C. Wolf, *ibid.*, **36**, 1727 (1971).

(16) Truce and Wolf (ref 12 and 15) have also observed that tosyl iodide addition to phenylallene gives the adduct of central attack by $ArSO_2$, *i.e.*, $C_6H_5CH{=}C(SO_2Ar)CH_2I$.

(17) L. R. Byrd and M. C. Caserio, *J. Amer. Chem. Soc.*, **92**, 5422 (1970).

(18) D. M. Golden, N. A. Gac, and S. W. Benson, *ibid.*, **91**, 2136 (1969).

Another noteworthy aspect of tosyl iodide addition to allenes is the selectivity of product formation. Whereas central attack by a tosyl radical could in principle lead to a mixture of isomeric allylic iodides, only one isomer is actually formed. Selectivity of this kind has also been observed in the addition of tosyl iodide to alkynes, giving a single 1:1 adduct by way of anti (trans) addition.[15] In the present case, the tosyl radical is evidently selective in its *direction* of approach as well as in its locus of attack, since either a cis or a trans adduct is formed but not both (Table II). Also, the intermediate allylic radicals react selectively in the atom-abstraction step to transfer iodine in all cases except one to the least substituted allylic terminus to form the product having the most highly substituted double bond (Table II). The one apparent exception is **6**, the adduct of 2-methyl-2,3-pentadiene, which is formed by iodine transfer to the most highly substituted allylic terminus. While it is entirely possible that product stability controls the observed selectivity in product formation, this cannot be established with certainty from the present data. In contrast, radical reagents such as HBr,[9] thiols,[10] and tin hydride[5] are less selective in the atom-transfer step of radical additions to allenes than is tosyl iodide, although the most stable of the possible adducts formed from these reagents are the major products.

**Addition of Halomethanes.**—The products of addition of iodomethane, iodotrifluoromethane, and bromotrichloromethane to 2,3-pentadiene show that carbon radicals $CH_3\cdot$, $CF_3\cdot$, and $CCl_3\cdot$ attack the terminal allenic carbons. Even in the case of 2-methyl-2,3-pentadiene, the only observable monoadducts reflect terminal attack by methyl radicals (Table IV). This is in distinct contrast to the behavior of tosyl iodide, which in every case except that for propadiene gave adducts of central attack by tosyl radicals. Bromotrichloromethane is apparently less selective than either $CH_3I$ or $CF_3I$, since adducts of central attack by $CCl_3\cdot$ were isolated from additions to 2,3-pentadiene, 2-methyl-2,3-pentadiene, and 1,2-cyclononadiene. The question of orientation is discussed further below.

**Orientation of Addition.**—The orientation data obtained in the present study (Tables II and IV) together with pertinent data taken from the literature is summarized collectively in Table I with respect to propadiene and 2,3-pentadiene. The most consistent feature is the high selectivity for central attack on 2,3-pentadiene by Br·, RO·, RS·, $R_3Sn\cdot$, and $RSO_2\cdot$. Radicals of the type $\cdot CX_3$ (X = H, F, Cl) are exceptional in showing a relatively high reactivity toward the terminal carbons of both propadiene and 2,3-pentadiene. Another general observation is the increase in reactivity of the central over the terminal positions with increasing methyl substitution, although this is less evident in the behavior of either $CH_3\cdot$ or $CF_3\cdot$ radicals.

Factors that have been considered as influential in determining the orientation in kinetically controlled radical additions to allenes include the electron distribution in the starting allene,[19] polarity of the attacking radicals,[20] steric effects, and the relative stabilities of the allylic and vinylic radicals formed. If the ground-state electron distribution in the allene were of singular importance, products of terminal attack should dominate.[19] Likewise, electrophilic radicals (*e.g.*, $CF_3\cdot$, Br·) should show a preference for terminal attack over so-called nucleophilic radicals (*e.g.*, $CH_3\cdot$, $R_3Sn\cdot$), but this is not supported by the data. Steric factors may be expected to favor central attack. In fact, changes in the orientation of addition of the halomethanes can reasonably be ascribed to steric effects. Whereas the carbon radicals $CF_3\cdot$, $CH_3\cdot$, and $CCl_3$ attack only the terminal position of propadiene, they behave differently toward the methyl-substituted allenes. Thus, the more highly substituted the allene and the larger the attacking radical ($CCl_3\cdot$), the greater the amount of adduct formed by way of central attack (Table IV).

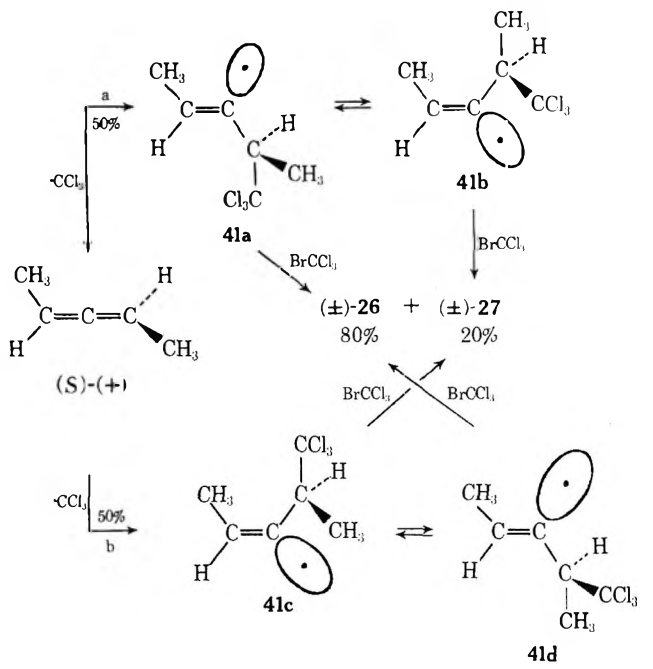
The extent to which the transition states leading to allylic and vinylic radicals are influenced by electronic factors is more difficult to evaluate. Our data clearly imply that planar allylic radicals are involved in the product-forming step of the central-attack pathway, but this does not exclude the possibility that the transition state for central attack has a twisted rather than a planar allylic configuration. In fact, the *lack* of selectivity exhibited by some radicals toward propadiene (Table I) requires that, in these cases at least, the two possible transition states must be closely balanced in energy, which suggests that the 10 kcal of resonance stabilization to be gained by the allylic system on achievement of coplanarity is *not* felt in the transition state for central attack. Other factors that may influence transition-state energies include hyperconjugation effects of terminal methyl groups and the higher strength of the bond forming between the attacking radical and the central carbon relative to the terminal carbon. These effects would both favor central radical attack, particularly in methyl-substituted allenes. On reflection then, it is somewhat surprising that methyl and trifluoromethyl radicals behave differently from all of the other radicals studied thus far in that they selectively attack the terminal positions of propadiene and its methyl analogs. The reasons for this seemingly anomalous behavior are not obvious and further discussion does not seem warranted at this time.

**Stereospecificity in $BrCCl_3$ Addition.**—The products obtained from bromotrichloromethane and (+)-2,3-pentadiene determine that $CCl_3\cdot$ radicals attack both terminal and central carbons. Recovery of unreacted (+)-2,3-pentadiene of *retained* optical purity assures that attack of $CCl_3\cdot$ at either site is essentially irreversible. The products, however, showed a small net rotation of $[\alpha]^{24}D$ −0.33° which may reasonably be ascribed to the adducts of terminal attack, **26** and **27**. That is, if the allylic bromide **28** is assumed to be racemic, the small residual activity in the products may be related to the stereospecificity of terminal attack, which is evidently low. Racemic or nearly racemic products are to be expected if the attacking radical is nonselective as to which side of the double bond it attacks (path a or b, Scheme I). Accepting this, the 80:20 mixture of racemic **27** and **26** may then be ex-

(19) Molecular orbital CNDO/2 calculations indicate that the charge density in propadiene and methyl analogs is greatest at the terminal carbons. This is supported by $^{13}C$ nmr data, which show the central carbons to be appreciably deshielded relative to the terminal carbons (J. K. Crandall, S. A. Sojka, and W. W. Conover, Indiana University, seminar presented at the International Symposium on Acetylenes, Allenes, and Cumulenes, University of Nottinham, July 1971).

(20) A. P. Stefani, L. Herk, and H. Szwarc, *J. Amer. Chem. Soc.*, **83**, 4732 (1961).

SCHEME I




plained in terms of initially formed vinyl radicals which rapidly equilibrate with their geometric isomers.[21] This is consistent with independent studies on α-alkylvinyl radicals, which in general appear to be configurationally unstable.[22,23] Thus, atom transfer to enantiomers **41a** and **41d** occurs 80% of the time to give (±)-**26** and to enantiomers **41b** and **41c** 20% of the time (apparently for steric reasons) to give (±)-**27** (Scheme I).

## Experimental Section

All the allenes used in this study were obtained from Matheson or Chemical Samples except for 2-methyl-2,3-pentadiene and 1,2-cyclononadiene. The former was prepared in 60% yield from 1,1-dibromo-2,2,3-trimethylcyclopropane[24] according to the method of Skattebøl;[25] 1,2-cyclononadiene was obtained in 87% yield from *cis*-9,9-dibromobicyclo[6.1.0]nonane by the method of Skattebøl and Solomon.[26] Partial resolution of 2,3-pentadiene and 1,2-cyclononadiene was achieved by the method described earlier.[2]

*p*-Toluenesulfonyl (tosyl) iodide was prepared (freshly before each use) in 90% yield from sodium *p*-toluenesulfinate dihydrate (Eastman, practical grade) and iodine according to a published procedure.[27] Methyl iodide (Mallinckrodt) and trifluoromethyl iodide (PCR, Inc.,) were analyzed by glpc (>99% pure) and used without treatment. Bromotrichloromethane (Aldrich) was distilled under nitrogen from molecular sieves prior to use.

**Addition of Tosyl Iodide.**—A typical procedure is given below for 3-methyl-1,2-butadiene. About 10.35 g (36.8 mmol) of tosyl iodide was dissolved in ~50 ml of anhydrous pentane in a 150-ml Fischer-Porter Pyrex high-pressure cylinder equipped with valves and pressure gauge. About 7.0 g (103 mmol) of 3-methyl-1,2-butadiene was weighed into the vessel and sufficient ether was added to ensure homogeneity. The resulting light orange solution was degassed, then irradiated for 30 min with a 250-W heat lamp positioned about 6 in. away. The color gradually faded to a pale yellow, at which time reaction was complete. The vessel was cooled to −78° to cause precipitation of the crystalline adduct. The cylinder was vented at room temperature, solvent and unreacted allene were decanted, and the product was blown dry with nitrogen. One recrystallization from 95% ethanol afforded 9.42 g (26.9 mmol, 73% based on tosyl iodide) of pale yellow crystals, mp 77–80°. Characterization of this and related adducts was based on ir, nmr (Table II), and solvolysis data (Table III). Configuration (cis or trans) was based on the observation that vinylic protons of vinyl sulfones are markedly deshielded (7.0–7.3 ppm) when cis to the sulfonyl group.[28]

Reaction with (*S*)-(+)-2,3-pentadiene was carried out as for the racemic material except that 15.0 g of a 42% (w/w) solution (6.3 g, 93 mmol) of partially resolved 2,3-pentadiene, $[\alpha]^{28}D$ 23.20 ± 0.05° (*c* 30, ether), and 5.82 g (20.6 mmol) of tosyl iodide were used. After the solution was heated for 30 min with the lamp, the ethereal solution of 2,3-pentadiene was decanted and distilled (6.1 g of a 38% solution in ether) and showed $[\alpha]^{28}D$ 21.61 ± 0.05° (*c* 27, ether). The crude adduct (7.0 g, 98%) showed no observable activity.

Reaction with (*S*)-(−)-1,2-cyclononadiene (10.0 g, 80 mmol), $[\alpha]^{28}D$ −23.20 ± 0.05° (neat), and 11.28 g (40 mmol) of tosyl iodide in ether was spontaneous and exothermic. The supernatant was dried ($MgSO_4$) and distilled to give 2.8 g of 1,2-cyclononadiene, bp 63–65° (11 mm), $[\alpha]^{28}D$ 0.46 ± 0.05° (neat). This residual rotation was attributed to a small amount of (+)-α-pinene carried over from the partial resolution. The crude adduct (13.8 g, 85%) showed no observable activity.

**Silver-Assisted Methanolysis of the Tosyl Iodide Adducts.**—An identical procedure was followed in the methanolysis of each of the adducts. A typical procedure for a particular adduct follows. To a solution of 3.50 g (10.0 mmol) of 3-tosyl-4-iodo-2-methyl-2-butene (**4**) in 50 ml of anhydrous methanol and 20 ml of $CHCl_3$ was added a solution of 2.05 g (13 mmol) of $AgBF_4$ in 25 ml of anhydrous methanol. Yellow silver iodide precipitated quantitatively and exothermically. The solution was filtered, 150 ml of ether was added, and the solution was washed successively with 50-ml portions of 10% aqueous $NaHSO_4$ (twice) and distilled water (five times). The solution was dried for 3 hr over anhydrous magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The yield of colorless, viscous oil was 2.50 g (9.8 mmol), 98% of theory based on starting adduct. Analysis by nmr was straightforward (Table III) and revealed a mixture of 3-tosyl-4-methoxy-2-methyl-2-butene (**10**) (61%) and 2-tosyl-3-methoxy-3-methyl-1-butene (**11**) (39%). Product percentages in this and all other methanolyses were determined directly by nmr integration.

**Addition of Methyl Iodide.**—A 6-in. quartz test tube was charged with a solution of 2.5 g (36.7 mmol) of (±)-2,3-pentadiene in 10.43 g (73.4 mmol) of methyl iodide. The solution was degassed and the tube was sealed at liquid nitrogen temperatures. The tube was suspended in a 150-ml quartz well containing iced water. The well itself was supported within the center of four parallel low-pressure mercury resonance lamps, 90% of the output being 253.7 nm (Ultraviolet Products, Inc.). After irradiation for 10 hr, the tube was opened at −78°. Unreacted methyl iodide and (±)-2,3-pentadiene were distilled away at atmospheric pressure and the residual material was distilled at 25° (5 mm) to give a volatile fraction constituting 23% of the total product mixture. Two 1:1 adducts were isolated from this fraction by preparative glpc in the ratio of 75:25. The major adduct was identified from its nmr spectrum (Table IV) as *trans*-3-iodo-4-methyl-2-pentene (**19**) and the minor adduct as the cis isomer **20**. Geometry was assigned from the fact that a vinylic proton cis to halogen is deshielded relative to a corresponding trans proton.[29] (*Cf.* the spectra of $CF_3I$ adducts **23**, **24**, and **25**.) The chemical shift of the methine heptet in both **19** and **20** is the same as that reported for a very similar compound, 2-iodo-3-methyl-1-butene.[30] Repetition of the above experiment in the presence of 0.95 g (12.2 mmol) of benzene as internal standard showed that 44% of the allene was consumed in

(21) Linear vinylic radicals **41** would also accommodate the results.

(22) O. Simamura in "Topics in Stereochemistry," Vol. 4, N. L. Allinger and E. L. Eliel, Ed., Wiley-Interscience, New York, N. Y., 1969.

(23) (a) L. A. Singer and N. P. Kong, *Tetrahedron Lett.*, 2089 (1966); *J. Amer. Chem. Soc.*, **88**, 5213 (1966); (b) J. A. Kampmeier and R. M. Fantazier, *ibid.*, **88**, 1959 (1966).

(24) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(25) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).

(26) L. Skattebøl and S. Soloman, *Org. Syn.*, **49**, 35 (1969).

(27) F. C. Whitmore and N. Thurman, *J. Amer. Chem. Soc.*, **45**, 1068 (1923).

(28) J. Uliana, D. Brundage, and M. C. Caserio, unpublished results, University of California, Irvine.

(29) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 138.

(30) S. A. Sherrod and R. G. Bergman, *J. Amer. Chem. Soc.*, **93**, 1925 (1971).

10 hr. The 1:1 adducts produced were completely inert to $AgBF_4$ in methanol.

Addition of methyl iodide to 2-methyl-2,3-pentadiene was carried out similarly. Glpc analysis revealed a very complex product mixture of which 26% corresponded to 1:1 adducts. These were isolated and identified as 3-iodo-2,4-dimethyl-2-pentene (**21**) (72%; ir 1624, 1374, and 1385 $cm^{-1}$) and *trans*-3-iodo-4,4-dimethyl-2-pentene (**22**) (28%; ir 3030, 1625 and 1362 $cm^{-1}$). The trans geometry for **22** was assigned by comparison of the chemical shift of the vinyl proton to that of **19**. Both **21** and **22** were inert to $AgBF_4$ in methanol.

**Addition of Trifluoromethyl Iodide.**—A 150-ml Fischer-Porter Pyrex high-pressure cylinder equipped with inlet and bleed valves and pressure gauge was charged with 3.0 g (44.1 mmol) of (±)-2,3-pentadiene. The tube was cooled to −78° and evacuated, and 15.2 (77.4 mmol) of trifluoromethyl iodide was condensed into the cylinder. The solution was degassed and then irradiated at 25° for 24 hr using a Hanovia medium-pressure mercury vapor uv utility lamp. The excess $CF_3I$ was vented and the unreacted allene was distilled away at atmospheric pressure (1.2 g, 40%). The slightly pink residue was taken up in 50 ml of ether and washed successively with 50-ml portions of 10% aqueous $Na_2S_2O_3$ (twice) and distilled water (twice). The colorless ethereal solution was dried over anhydrous $MgSO_4$ and filtered, and the ether was removed by rotary evaporation at 100 mm. The residual liquid was flash distilled at 25–40° (0.5 mm) to give 4.32 g of a colorless, fruity-smelling liquid, trapped at −78°, and about 2.3 g of a dark resinous material which could not be distilled. Analysis by glpc revealed a very complex mixture of products, including three major volatile products comprising about 44% of the total. The 1:1 adduct fraction was isolated virtually free from higher molecular weight products by flash distillation at room temperature (10 mm). The three suspected 1:1 adducts were isolated by preparative glpc. The most volatile and least abundant product (9%) was identified as *trans*-3-iodo-2-pentene (**23**). Geometry was assigned by comparison of $\delta_a$, $\delta_b$, and $J_{ab}$ with those of similar compounds **19** and **22** (Table IV). The compound was inert to methanolic $AgBF_4$; ir 1638 $cm^{-1}$ (C=C), 200–450 $cm^{-1}$ (C–I). Its $^{19}F$ nmr spectrum was transparent within the range accessible by the spectrometer. The major adduct (70% of mixture of 1:1 adducts) was characterized as *trans*-3-iodo-4-trifluoromethyl-2-pentene (**24**) on the basis of its $^1H$ and $^{19}F$ nmr and ir spectra. Geometry was assigned by analogy to the cis–trans vinyl iodide isomers previously characterized (*cf.* **19**, **22**, **23**, Table IV). Orientation was confirmed by the inertness to methanolic $AgBF_4$ and also by the magnitude of $J_{HF}$. The value of 8.8 Hz (Table IV) derived from the $^{19}F$ doublet is entirely consistent with a vicinal H–F interaction but incompatible with an H–F interaction through three carbon atoms.[31] Its ir spectrum showed 1630 (C=C), 1130, 1175, 1255 (C–F), 900, 955, 1000 $cm^{-1}$ (=CH bend). The minor 1:1 adduct was similarly characterized as *cis*-3-iodo-4-trifluoromethyl-2-pentene (**25**). Its ir spectrum showed 1620 (C=C), 1120, 1165, 1255 (C–F), 900, 955, 955 $cm^{-1}$ (=CH bend). Several of the higher molecular weight products were isolated by preparative glpc and examined by $^1H$ and $^{19}F$ nmr spectroscopy. The spectra were very complex and in no case could they be correlated to 1:1 adducts of opposite orientation, 2:1 adducts of either orientation, or secondary photoproducts derived in any simple fashion from the observed 1:1 adducts.

**Addition of Bromotrichloromethane to (±)-2,3-Pentadiene.**—A 100-ml round-bottom flask equipped with thermometer, reflux condenser, and magnetic stirrer was charged with 10.0 g (0.147 mol) of (±)-2,3-pentadiene, 50.0 g (0.253 mol) of bromotrichloromethane, and 0.57 g (0.0024 mol) of benzoyl peroxide. The mixture was stirred at room temperature until solution of the peroxide was complete, then gradually heated to 80°, whereupon gentle reflux began. The reaction mixture was refluxed for 2.5 hr, during which time the temperature of reflux reached 95°. Unreacted hydrocarbon and bromotrichloromethane were removed by flash distillation at 25–40° (1 mm). The residual sweet-smelling liquid was distilled *in vacuo* at 0.5 mm to give three fractions: (1) 55–60°, 4.50 g; (2) 60–65°, 10.4 g; (3) 65–68°, 21 g. Each of the fractions showed clearly by nmr a mixture of three 1:1 adducts, and so were combined. Isolated yield of product oil is 61% based on starting allene.

The orientation of two of the adducts was assigned as **26** and **27** by reason of their inertness toward methanolic silver tetrafluoroborate. Their nmr spectra, in particular the chemical shifts of their methine quartets ($\delta_c$ 3.50, 3.77, Table IV) are compatible with allylic $CX_2$ (*cf.* **24**, **25**, Table V) but incompatible with allylic Br (*cf.* **28**, **31**, Table IV). By analogy to **24**, **25** and **19**, **20**, trans geometry was assigned to the major terminal attack adduct **27** (47%) and cis to the minor isomer **26** (12%).

Addition of $BrCCl_3$ to 2-methyl-2,3-pentadiene was carried out similarly; 12.06 g (0.147 mol) of hydrocarbon, 50.00 g (0.253 mol) of $BrCCl_3$, and 1.0 g (0.0041 mol) of benzoyl peroxide were refluxed (80–85°) for 2 hr. After distillation to remove unreacted materials, the mixture was distilled *in vacuo*. The major fraction (18.50 g), bp 80–88° (0.1 mm), corresponded to compounds **29** and **30** (Table IV). The structures assigned are supported by the structures of the methanolysis products (Table V) and from their mass spectra: **29** showed *m/e* 278, 280, 282, 284 in the ratio of 1:2:1.3:0.3 and corresponds to $M^+$ containing the elements $BrCl_3$; **30** showed *m/e* 198, 200, and 202 in the ratio 1:1:0.3 for $M^+$ containing three chlorines.[32]

Reaction of $BrCCl_3$ with 1,2-cyclononadiene in the mole ratio of 2:1 gave a quantitative conversion to adduct **31** after 2 hr at 75° in the presence of benzoyl peroxide.

**Silver-Assisted Methanolysis of Halomethane Adducts.**—Reactions were carried out essentially as described previously for the tosyl iodide adducts. The structures assigned the products are shown in Table V along with the nmr data. Compounds **19**–**27** failed to react, consistent with the absence of allylic halogen. The mass spectrum of the product obtained from **28** showed *m/e* 180, 182, 184 in the ratio of 65:41:7, corresponding to $M^+$ containing two chlorines. The fragmentation on electron impact and the nmr spectrum support the assigned structures as **32** and **33** corresponding to solvolysis of allylic chlorine and bromine. Solvolysis of **29** gave **34** (*m/e* 230, 232, 234 in ratio 1:1:0.3), and **30** gave **35** for which no parent molecular ion was observed in its mass spectrum. Solvolysis of **31** gave a complex mixture which could not be analyzed satisfactorily.

**Registry No.**—**1**, 35890-15-4; **2**, 35925-44-1; **3**, 35890-16-5; **4**, 35890-17-6; **5**, 35890-18-7; **6**, 35890-19-8; **7**, 35890-20-1; **8**, 35890-21-2; **9**, 35890-22-3; **10**, 35890-23-4; **11**, 35890-24-5; **12**, 35890-25-6; **13**, 35890-26-7; **14**, 35890-27-8; **15**, 35890-28-9; **16**, 35890-29-0; **17**, 35890-30-3; **18**, 35895-34-2; **19**, 35895-35-3; **20**, 35895-36-4; **21**, 35895-37-5; **22**, 35895-38-6; **23**, 35895-39-7; **24**, 35895-40-0; **25**, 35895-41-1; **26**, 35895-42-2; **27**, 35895-43-3; **28**, 35895-44-4; **29**, 35895-45-5; **30**, 35895-46-6; **31**, 35895-47-7; **32**, 35895-48-8; **33**, 35895-49-9; **34**, 35895-50-2; **35**, 35925-45-2; propadiene, 463-49-0; 1,2-butadiene, 590-19-2; 3-methyl-1,2-butadiene, 598-25-4; 2,3-pentadiene, 591-96-8; 2-methyl-2,3-pentadiene, 3043-33-2; 1,2-cyclononadiene, 1123-11-1.

(31) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 222.

(32) J. H. Beynon, R. A. Saunders, and A. E. Williams, "The Mass Spectra of Organic Molecules," Elsevier, Amsterdam, 1968, p 376.

# Reactions of α-Ketolic and Other 21-Hydroxy Steroids with Phosgene. I. Preparation and Properties of Bis(pregnan-21-yl) Carbonates and 17,21-Cyclic Carbonates[1]

MARVIN L. LEWBART

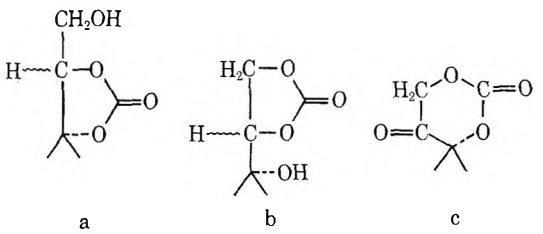
*Department of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania 19107*

*Received June 16, 1972*

Reaction of phosgene in benzene with excess α-ketolic steroids in pyridine at 0° affords symmetrical bis(pregnan-21-yl) carbonates in good yield; binary mixtures of α-ketols give mixed carbonates in low yield. The new bisteroidal carbonates are stable to chromic anhydride–pyridine and strong mineral acid, but are readily cleaved to the parent α-ketols in weak alkali. Reaction of 11-deoxycortisol with excess phosgene results in excellent conversion to the 21-chlorocarbonate, but this product is quantitatively hydrolyzed to starting material during the work-up. In contrast, reaction of cortisone with excess phosgene provides the 17,21-cyclic carbonate **21** in 36% yield. Refluxing **21** in methanol affords both the 21-camylate **19** and a novel rearrangement product, the 20β-methoxy 17,20α-cyclic carbonate **22**. The formation of the latter compound can readily be understood in terms of a four-center-type mechanism. A number of nonketolic 17,21-diols also react with phosgene; the relative amounts of 21,21′-bisteroidal and 17,21-cyclic carbonates formed are determined both by the reaction conditions and the nature of the substituent at C-20.

We recently described[2] the preparation of five-membered ring 17,20- and 20,21-cyclic carbonates (partial formulas a and b, respectively, Scheme I) from the

SCHEME I



a b c

glycerol side chain. It seemed of interest to extend these studies to the synthesis of six-membered ring 17,21-cyclic carbonates (c) from the dihydroxyacetone side chain. However, it became evident as the work progressed that, although a 17,21-cyclic carbonate of type c could be prepared under suitable conditions, other products of both practical and theoretical interest are formed when α-ketols react with phosgene. The scope of this investigation was therefore enlarged to include the reactions of 17-deoxy-α-ketols and other 21-ols with various substituents at C-20. In this paper will be described the preparation and reactions of 21,21′-bisteroidal carbonates and 17,21-cyclic carbonates.

When a solution of cortisone in pyridine was treated with phosgene in benzene under conditions suitable for the preparation of a and b, *i.e.*, the slow addition of reagent to excess steroid at 0° (condition A), the major product (83%) was not the expected 17,21-cyclic carbonate. Infrared analysis showed significant hydroxyl absorption and a new carbonyl band of moderate intensity at 1760 $cm^{-1}$. The product reduced alkaline blue tetrazolium and, although unaffected by methanolic cupric acetate and acetic anhydride–pyridine, it was readily converted to starting material in alkaline methanol. On the basis of these properties and a confirmatory molecular weight determination [calculated, 747; found, 791 (thermoelectric)], the product was identified as bis(cortison-21-yl) carbonate (**1**) (Table I).

As far as we are aware, the only other bisteroidal carbonate described previously is that from cholesterol.[3] For this reason a number of symmetrical carbonates having in common the $\Delta^4$-3-one grouping were prepared under condition A. Constants obtained for bisteroidal carbonates from cortisol, 11-deoxycortisol, 11-dehydrocorticosterone, corticosterone, and 11-deoxycorticosterone (**2**–**6**, respectively) are given in Table I. Yields from 11-deoxy- and 11-keto-α-ketols averaged from 70 to 80%, but those from the two 11β-ols were significantly lower because of the formation in 15–20% yield of mixed carbonates **7** and **8** of the parent α-ketols and their $\Delta^{9,11}$ dehydration products. Structural assignments for mixed carbonates **7** and **8** were made by examination of the cleavage products generated in alkaline methanol.[4]

Mixed carbonates could also be prepared in low yield by treating equivalent amounts of different α-ketols under condition A. For example, reaction of a mixture of cortisol and 11-deoxycorticosterone gave, in addition to the symmetrical carbonates **2** and **6**, a product with intermediate chromatographic mobility. Its identity as cortisol-21-yl-11-deoxycorticosteron-21′-yl carbonate (**9**) was established by alkaline hydrolysis to roughly equal amounts of the parent α-ketols. Similar treatment of mixtures of cortisone and 11-deoxycorticosterone and of corticosterone and 11-deoxycorticosterone provided mixed carbonates **10** and **11**, respectively.

The chemical properties of the new bisteroidal carbonates are similar to those of five-membered ring cyclic carbonates. The stability of the carbonate bond to chromic anhydride–pyridine was demonstrated by oxidizing the 11β-ols **2**, **5**, **9**, and **11** to the corresponding 11-ones **1**, **4**, **10**, and **12**. Bisteroidal carbonates are readily cleaved by weak alkali, but are very resistant to mineral acids. For example, refluxing a solution of **1** in 3 *N* 90% ethanolic sulfuric

(1) This work was supported by a research grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).

(3) F. Schadendorff and A. Verdino, *Monatsh.*, **65**, 338 (1935).

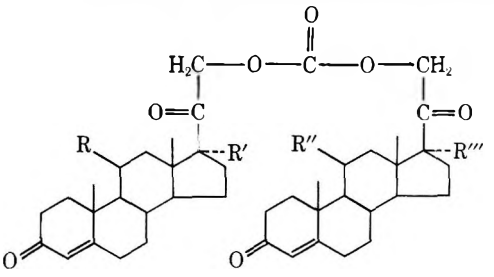
(4) The acetylated hydrolysis products from **7** were identified as cortisol acetate and 17-hydroxy-21-acetoxypregna-4,9(11)-diene-3,20-dione.[5] The corresponding products from **8** were corticosterone acetate and 21-acetoxypregna-4,9(11)-diene-3,20-dione.[6]

(5) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **79**, 1130 (1957). The author is indebted to Dr. Walter R. Benn of G. D. Searle & Co. for a reference sample of this compound.

(6) C. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

TABLE I

STRUCTURES AND CONSTANTS OF BIS(20-OXOPREGNEN-21-YL) CARBONATES

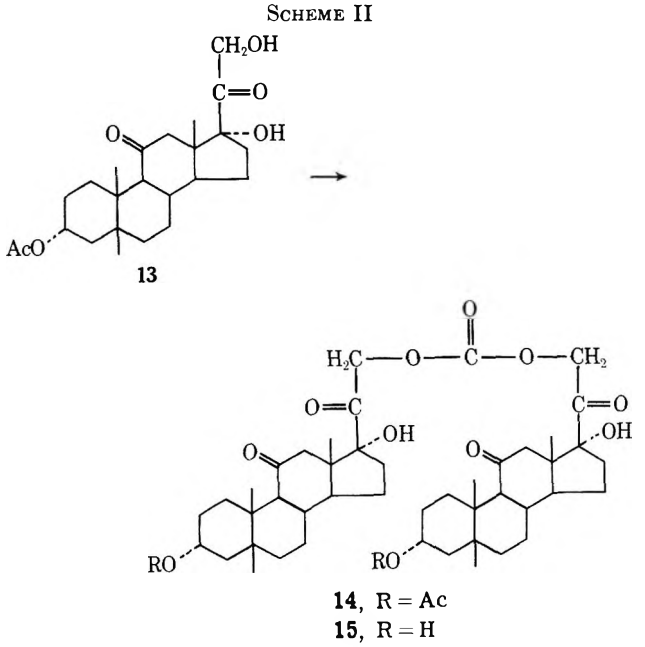


| Compd | R | R′ | R″ | R‴ | Mp, °C | [α]D | λmax, mμ | ε | νmax, cm⁻¹ | Empirical formula | Calcd,[a] % C | Calcd,[a] % H | Found, % C | Found, % H | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | =O | OH | =O | OH | 235–237 | +268 | 238 | 30,400 | 1760, 1275, 785 | $C_{43}H_{54}O_{11}$ | 69.15 | 7.29 | 68.86 | 7.34 | 83 |
| 2 | β-OH | OH | β-OH | OH | 193–194 | +215 | 242 | 30,800 | 1755, 1285 789 | $C_{43}H_{58}O_{11}$ | 63.45 | 8.05 | 63.42 | 8.11 | 56 |
| 3 | H | OH | H | OH | 275–276 | +218[b] | 241 | 31,400 | 1762, 1290, 785 | $C_{43}H_{58}O_9$ | 71.84 | 8.13 | 71.66 | 8.22 | 82 |
| 4[c] | =O | H | =O | H | 136–139 | +290 | 238 | 31,300 | 1763, 1272 789 | $C_{43}H_{54}O_9$ | 72.24 | 7.61 | 72.23 | 7.71 | 68 |
| 5 | β-OH | H | β-OH | H | 256–259 | +253 | 241 | 29,700 | 1760, 1275, 790 | $C_{43}H_{58}O_9$ | 71.84 | 8.13 | 71.71 | 8.16 | 50 |
| 6 | H | H | H | H | 115–118 | +194 | 240 | 29,200 | 1760, 1270, 786 | $C_{43}H_{58}O_7$ | 72.34 | 8.61 | 72.30 | 8.23 | 84 |
| 7 | Δ9,11 | OH | β-OH | OH | 178–180 | +188 | 241 | 31,400 | 1759 1278, 785 | $C_{43}H_{56}O_{10}$ | 68.78 | 7.79 | 68.54 | 7.82 | 20 |
| 8 | Δ9,11 | H | β-OH | H | 134–135 | +220 | 241 | 29,700 | 1760, 1275, 790 | $C_{43}H_{56}O_8$ | 73.68 | 8.05 | 73.55 | 8.08 | 15 |
| 9 | H | H | β-OH | OH | 154–156 | +202 | 242 | 29,700 | 1759, 1278, 785 | $C_{43}H_{58}O_9$ | 66.81 | 8.35 | 66.95 | 7.95 | 29 |
| 10 | H | H | =O | OH | 231–234 | +250 | 240 | 31,400 | 1759, 1272 785 | $C_{43}H_{56}O_9$ | 72.04 | 7.87 | 71.89 | 7.89 | 22 |
| 11 | H | H | β-OH | H | 135–137 | +224 | 241 | 31,500 | 1760, 1270, 785 | $C_{43}H_{58}O_8$ | 68.89 | 8.46 | 70.27 | 8.10 | 27 |
| 12[c] | H | H | =O | H | 129–131 | +250 | 240 | 31,400 | 1760, 1270, 785 | $C_{43}H_{56}O_8$ | 73.68 | 8.05 | 73.37 | 7.97 | 62[d] |

[a] Calculated values for compounds **2**, **6**, **7**, **9**, and **11** include 3.5, 1.5, 1, 3, and 2 molecules of water, respectively. [b] Determined in chloroform–methanol (1:1). [c] Obtained as a filterable solid from aqueous methanol. The remaining compounds were crystallized from methanol. [d] Indicates yields from chromic anhydride–pyridine oxidation of **11**.

acid for 2 hr was without effect. Advantage was taken of this property in the synthesis of bis(tetrahydrocortison-21-yl) carbonate (**15**) (Scheme II). Reaction

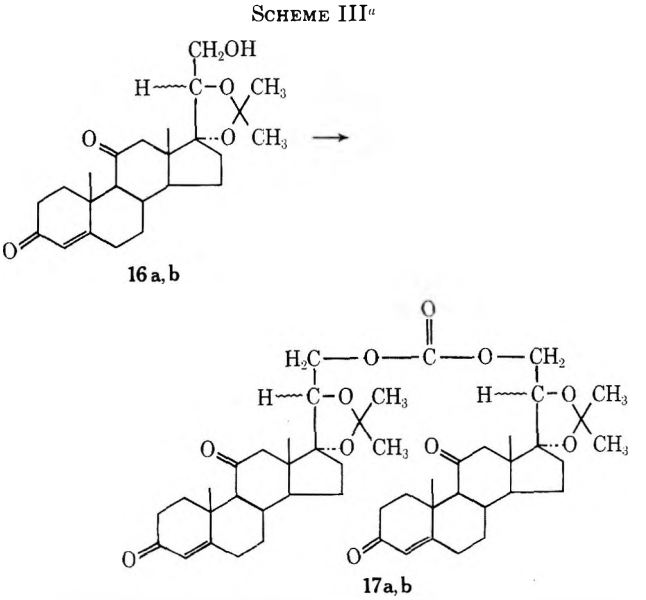
SCHEME II



of tetrahydrocortisone 3-monoacetate (**13**) with phosgene under condition A afforded the 3,3′-diacetate **14** in 80% yield. Treatment of **14** with methanolic sulfuric acid at room temperature resulted in deacetylation only, providing the 3,3′-diol **15** in 85% yield.

The extraordinary resistance to acid hydrolysis of the carbonate bond suggested a possible route to 21,21′-bisteroidal carbonates derived from the glycerol side chain. Since we had shown previously that some 17,20-acetonides can be cleaved by aqueous acetic acid,[7] it was hoped that phosgenation of the 21-ols followed by selective deacetonation would afford the desired bis(17,20-dihydroxypregnan-21-yl) carbonates. Accordingly, the 17,20-acetonides **16a** and **16b**[8] (Scheme III)

SCHEME III[a]

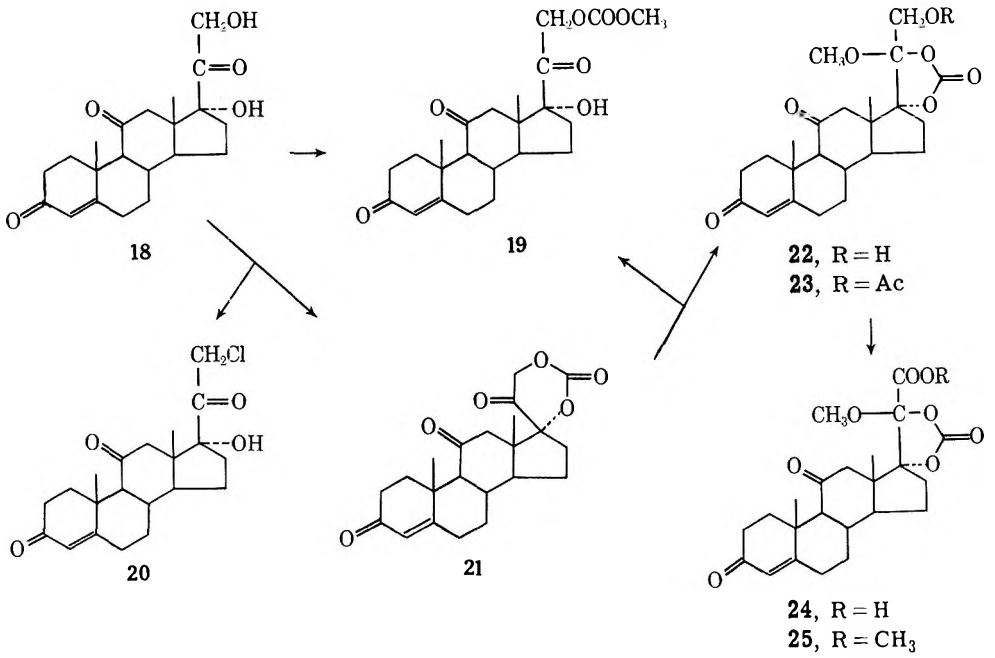


[a] The substituent at C-20 is α oriented in a compounds and β oriented in b compounds.

were converted to the corresponding bisteroidal carbonates **17a** and **17b** in yields of nearly 90%. Treatment of **17a** in 80% acetic acid for 24 hr at 65° resulted in its complete transformation to three identifiable products. These are 20α,21-cyclocarbonyldioxy-17-

(7) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).
(8) M. L. Lewbart and J. J. Schneider, *ibid.*, **34**, 3513 (1969).

SCHEME IV




hydroxypregn-4-ene-3,11-dione[8] (52%), 17,20α,21-trihydroxypregn-4-ene-3, 11-dione (32%), and 21-acetoxy-17,20α-dihydroxypregn-4-ene-3,11-dione (6%). In agreement with our earlier observations on the greater difficulty in hydrolyzing 17,20β-acetonides,[7] treatment of **17b** under the same conditions employed for **17a** had no effect. However, refluxing the 20β epimer in the same solvent for 8 hr resulted in nearly 75% loss of starting material. The two chief products which could be recovered are 17,20β-cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione[8] (14%) and 17,20β,21-trihydoxypregn-4-ene-3,11-dione (12%). These results indicate that under the conditions employed both carbonate and acetonide bonds are ruptured, and, although the generation of cyclic carbonates as major products is of some interest, it is evident that selective deacetonation can not be achieved by this approach.

In the course of these investigations phosgenation of 11-deoxycortisol was carried out in a reverse manner, *i.e.*, by the slow addition of steroid in pyridine to a large excess of phosgene in benzene at 0° (condition B). It was found that under this condition the bisteroidal carbonate **3** is a minor product, and starting material was recovered in nearly quantitative yield. It was shown in a separate experiment, however, that, if methanol instead of ice is added to decompose excess reagent, the 21-*O*-carbomethoxy derivative (camylate) could be isolated in 88% yield. These findings suggest that, although a 21-chlorocarbonate is formed, it is quickly hydrolyzed in the course of the work-up. On the other hand, reaction of cortisone (**18**, Scheme IV) under condition B provided very little starting material after the usual work-up. The 21-chlorocarbonate is also evidently a minor product, since addition of methanol to a reaction mixture provides cortisone 21-camylate (**19**) in only 20% yield. Another minor product (10%) was identified as the 21-chloride **20**.[9] The major product (36%) from the reaction of cortisone with excess phosgene is the 17,21-cyclic carbonate **21**. This structural assignment is based chiefly on infrared analysis, which shows the absence of hydroxyl and the presence of a new carbonyl band at 1770 $cm^{-1}$. Treatment of **21** with methanolic potassium bicarbonate regenerated the α-ketol **18**.

In comparing the behavior of 11-deoxycortisol and cortisone under condition B, it is apparent that, although both α-ketols are converted to chlorocarbonates, the subsequent fate of these respective intermediates is strikingly different. Our results suggest that the 11-deoxy chlorocarbonate is unable to undergo elimination of hydrogen chloride followed by 17,21 cyclization, and is therefore completely hydrolyzed to starting material during the work-up. It would therefore appear that spontaneous dehydrochlorination leading to 17,21 cyclization occurs only in the presence of a carbonyl group at C-11.

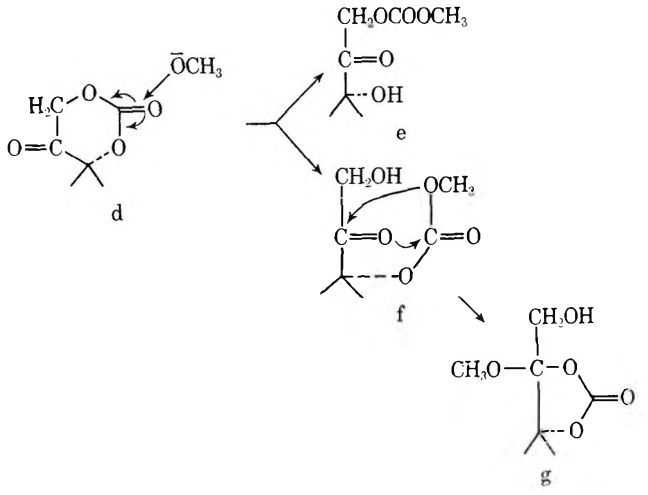
In the course of manipulating the cyclic carbonate **21** in methanol it was noted that prolonged heating brought about generation of two chromatographically less mobile artifacts. Refluxing **21** in methanol for 19 hr resulted in its complete conversion to roughly equal amounts of these two products. The mixture was resolved by silica gel column chromatography into a major mobile component (54%), the 21-camylate **19**, and a minor polar substance (19%). Since the latter product was found to have limited stability on silica gel, the low yield does not reflect the amount originally present in the reaction mixture. Organic microanalysis and mass spectroscopy showed that the unknown product contains one methoxyl group and is isomeric with the 21-camylate **19**. The presumption that it is the 17-camylate was supported by its conversion to a monoacetate under mild conditions. However, the infrared spectrum of the minor product exhibited strong bands at 1810 and 790 $cm^{-1}$ which are characteristic of five-membered ring cyclic carbonates.[2] On the basis of these findings the compound is formulated as the 20-methoxy 17,20-cyclic carbonate **22** and its acetate as **23**. This structural assignment was substantiated by

(9) The author thanks Dr. Norman G. Brink of Merck Research Laboratories for a reference sample of 21-chloro-17-hydroxypregn-4-ene-3,11,20-trione.

the oxidation of 22 with chromic anhydride in acetic acid to the pregnenoic acid 24, which was further characterized as the methyl ester 25.

A plausible mechanism which explains the formation of the 21-camylate 19 and the methoxy cyclic carbonate 22 from 21 involves initial attack by methoxide ion on the carbonate carbonyl (d, Scheme V) with re-

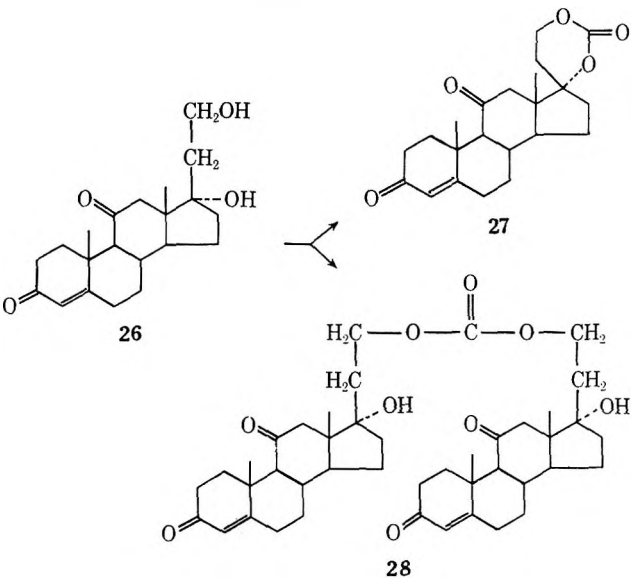
Scheme V



sultant ring opening and generation in equal amounts of the 21- and 17-camylates e and f. Further reaction of the 17-camylate occurs by a four-center-type mechanism[10] in which attack by the C-20 carbonyl oxygen on the carbonate carbonyl is accompanied by migration of the methoxyl group to C-20, affording g. A point of special interest in the step from f to g is the stereospecific nature of the rearrangement. Nmr analysis indicated the presence of only one C-20 epimer, but attempts to establish the configurations of the substituents at C-20 by this technique were unsuccessful.[11] However, examination of a Dreiding model of the 17-camylate f reveals that under the postulated mechanism close approach of the reacting carbonyl groups can occur only when the hydroxymethylene group at C-21 is facing toward the angular methyl at C-18, *i.e.*, in the configuration assumed by 17,20α-cyclic carbonates.[2] This would restrict migration of the methoxyl group to the 20β position, giving the configuration for 22 and its derivatives as indicated in Scheme IV. Additional support for this configurational assignment was obtained when it was noted that the average of the molecular rotations of the four methoxy cyclic carbonates 22–25 (+431 units) is in much closer agreement with that of the corresponding C-20-unsubstituted 17,20α-cyclic carbonates (+382 units) than that of their 20β epimers (+687 units).

The synthesis of cortisone 17,21-cyclic carbonate 21 in modest yield prompted a study to determine the influence of a given substituent at C-20 on the relative amounts of bisteroidal and cyclic carbonates afforded by 17,21-diols under conditions A and B. A major aim of the investigation was to ascertain to what extent the C-20 carbonyl group facilitates or interferes with 17,21 cyclization. The simplest representative in this series, 20-deoxycortisone[12] (26, Scheme VI), afforded

Scheme VI



the 17,21-cyclic carbonate 27 in 85% yield after being phosgenated under condition B. Structural assignment was based on the same considerations applied to the corresponding 20-one 21. Unlike the cortisone derivative, 27 was stable to refluxing methanol but, like 21, was readily hydrolyzed in alkaline methanol. When the 17,21-diol 26 was treated under condition A, the yield of cyclic carbonate 27 fell to 61%, and a less mobile substance (12.5%) could also be recovered. This minor product was identified as bis(20-deoxycortison-21-yl) carbonate (28) because it exhibits the same characteristic infrared bands seen in its α-ketolic counterparts. One must conclude from these findings that the presence of a C-20 carbonyl group serves to inhibit 17,21 cyclization, since the 20-deoxy analog cyclic carbonate 27 is obtained as the major product even under conditions which bring about conversion of α-ketols to their bisteroidal carbonates in yields exceeding 80%.

The reaction with phosgene of 11-deoxycortisol 3,20-bisketal[13] (29, Scheme VII) and cortisone 3,20-bisketal[14] (30) was also studied. Treatment of 29 and 30 under condition B gave their respective 17,21-cyclic carbonates 31 and 32 in virtually quantitative yields. Treatment of 31 and 32 with *p*-TSA in acetone at room temperature resulted in selective deketalization at C-3, providing the corresponding $\Delta^4$-3-ones 33 and 34. Attempts to remove the remaining ketal group at C-20 without altering the cyclic carbonate ring were not successful. When the bisketals 29 and 30 were phosgenated under condition A, roughly equal amounts of the 17,21-cyclic carbonates 31 and 32 and the bisteroidal carbonates 35 and 36 were obtained. These findings are of interest for two reasons. First, they demonstrate that, in comparison with the reactions of 20-keto- and 20-deoxy-17,21-diols, 20-ethylene ketals show inter-

(10) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 457.

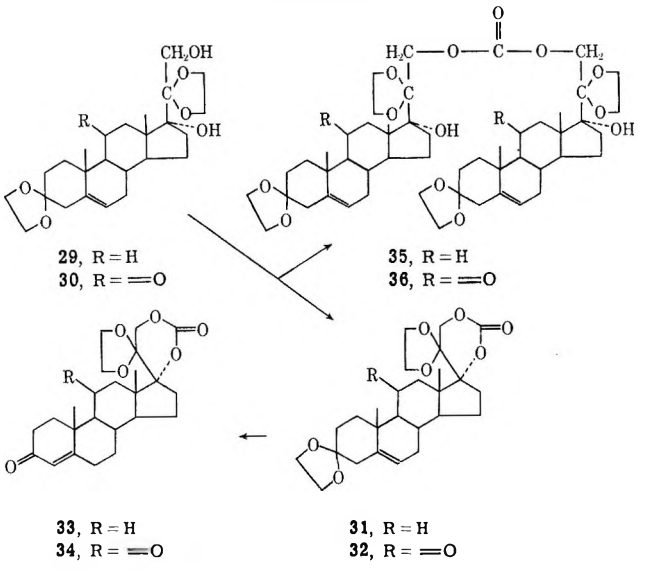
(11) We wish to thank Dr. Byron H. Arison of Merck Research Laboratories for the determination and interpretation of the nmr spectra.

(12) M. L. Lewbart, *J. Org. Chem.*, **37**, 1224 (1972).

(13) R. Antonucci, S. Bernstein, and R. H. Lenhard, *J. Amer. Chem. Soc.*, **76**, 2956 (1954).

(14) R. Antonucci, S. Bernstein, M. Heller, R. H. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

SCHEME VII




mediate tendencies when phosgenated under condition A. Second, the presence of an ethylene ketal group at C-20 serves to eliminate the marked difference in behavior observed in the reactions of 11-deoxycortisol and cortisone under condition B.

The infrared spectral properties of the new bisteroidal and 17,21-cyclic carbonates were examined with the aim of establishing characteristic group frequencies. All symmetrical and mixed linear carbonates exhibited an expectedly diminished carbonyl band ranging from 1766 to 1754 $cm^{-1}$. The only exception was observed for the 20-deoxycortisone derivative **28** (1749 $cm^{-1}$). Like side-chain cathylates and five-membered ring cyclic carbonates,[2] all bisteroidal carbonates possess a medium to strong band in the region from 790 to 785 $cm^{-1}$. However, the very strong band which cathylates exhibit at 1265–1260 $cm^{-1}$ is shifted to a significantly higher frequency (1290–1266 $cm^{-1}$) in bisteroidal carbonates. Within the restrictions imposed by the limited number of samples available, it appears that the absorption frequency of the carbonate carbonyl in six-membered ring cyclic carbonates depends upon the degree of ring strain imposed by the substituent at C-20. As would be predicted, the highest frequency (1775 $cm^{-1}$) was observed in the 20-ketone **21** and the lowest in the 20-deoxy cyclic carbonate **27** (1745 $cm^{-1}$). Intermediate carbonyl frequencies centering at 1755 $cm^{-1}$ are exhibited by the four ethylene ketals **31–34**. The only band in the fingerprint region which all six 17,21-cyclic carbonates have in common is a very strong one at 1115–1110 $cm^{-1}$, but, since ethylene ketals also absorb strongly in this region, this assignment is only tentative.

## Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined at 365 and 589 mμ (D line of sodium) in a Ziess 0.005° photoelectric polarimeter. Unless noted otherwise measurements were made in chloroform solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ±1°. Infrared (ir) spectra were determined as KBr pellets with a Beckman IR-8 instrument. Nmr spectra were determined with a Varian HA-100D instrument in $CDCl_3$, using TMS as an internal standard. Ultraviolet (uv) spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. General procedures for column and thin layer (tlc) chromatographic techniques and the processing of reaction mixtures have been cited earlier.[7] In those cases where column chromatography was required for bisteroidal carbonates from α-ketols, such as in the preparation of mixed carbonates **7–11**, Zaffaroni-type systems[15] were employed, since compounds of this type appear to have limited stability on silica gel. Microanalyses were by August Peisker-Ritter, Brugg, Switzerland, and Alfred Bernhard, Elbach über Engelskirchen, West Germany.

**General Procedures for the Phosgenation of 21-Hydroxy Steroids. Condition A.**—To a stirred solution of steroid (1 mmol) in pyridine (5 ml) at 0° was added dropwise a 3.75% solution of phosgene in benzene (5 ml) over a 20-min period. After the solution was stirred for another 5 min at 0°, methylene chloride (50 ml) and ice were added, and the product was recovered by successive washing with cold hydrochloric acid and water.

**Condition B.**—To a stirred 6.25% solution of phosgene in benzene (10 ml) at 0° is added dropwise 1 mmol of steroid in pyridine (10 ml) over a 20-min period. Decomposition of excess reagent and recovery of the product were carried out as in condition A.

**17,21-Dihydroxy-3α-acetoxy-5β-pregnane-11,20-dione (13) from Tetrahydrocortisone 3,21-Diacetate.**—To a solution of 17-hydroxy-3α,21-diacetoxy-5β-pregnane-11,20-dione (1792 mg, 4 mmol) in a mixture of methanol (180 ml) and methylene chloride (40 ml) was added 1 *N* aqueous sodium hydroxide (0.3 ml). After 2 hr at room temperature 9 drops of acetic acid was added, and the solution was concentrated *in vacuo*. The crude product was chromatographed on a 41 × 800 mm Celite column in chloroform (100 ml), toluene (100 ml), and formamide (5 ml). Fractions (12 ml) were collected every 10 min. The contents of fractions 57–80 crystallized from methanol as long needles (800 mg, mp 195–198°; 90 mg, mp 189–193°) in a yield of 67%: $[\alpha]_{365}$ 412°; $[\alpha]_D$ 92.9°; $\nu_{max}$ 1730 (sh), 1245, and 1032 $cm^{-1}$ (3α-acetate).

*Anal.* Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.82; H, 8.21.

**Bis(17-hydroxy-3α-acetoxy-11,20-dioxo-5β-pregnan-21-yl) Carbonate (14) from 13.**—Phosgenation of 17,21-dihydroxy-3α-acetoxy-5β-pregnane-11,20-dione (406 mg, 1 mmol) was carried out under condition A. The reaction mixture was chromatographed on a 20 × 750 mm Celite column in toluene (100 ml), isooctane (100 ml), and formamide (5 ml), collecting 5-ml fractions. After the emergence of fraction 295, the system was changed to toluene (200 ml), isooctane (100 ml), and formamide (5 ml). Crystallization from acetone of the residue from fractions 416–425 gave hairy needles (335 mg, 80%): mp 175–177°; $[\alpha]_{365}$ 544°; $[\alpha]_D$ 120°; $\nu_{max}$ 3490 (hydroxyl), 1740 (sh), 1245, 1035 (3α-acetate), 1765, 1273, and 796 $cm^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{47}H_{66}O_{13}$: C, 67.28; H, 7.93; $CH_3CO$, 10.26. Found: C, 67.43; H, 8.01; $CH_3CO$, 9.83.

**Bis(3α,17-dihydroxy-11,20-dioxo-5β-pregnan-21-yl) Carbonate (15) from 14.**—To a solution of bis(17-hydroxy-3α-acetoxy-11,20-dioxo-5β-pregnan-21-yl) carbonate (100 mg) in 90% aqueous methanol (100 ml) was added 8 ml of concentrated sulfuric acid. After 66 hr at room temperature anhydrous sodium acetate (28 g) was added, the reaction mixture was diluted with methylene chloride (500 ml), and the solution was washed twice with water. Crystallization of the dried residue from methanol–ether gave 76 mg (85%) of rosettes: mp 196–197°; $[\alpha]_{365}$ 594°; $[\alpha]_D$ 112°; $\nu_{max}$ 3450 and 1242 (3α-hydroxyl), 1765, 1285, and 790 $cm^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{43}H_{62}O_{11}$: C, 68.41; H, 8.28. Found: C, 68.58; H, 8.41.

**Bis(17,20α-isopropylidenedioxy-3,11-dioxopregn-4-en-21-yl) Carbonate (17a) from 16a.**—Reaction of 17,20α-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione[8] (1010 mg, 2.5 mmol) was carried out under condition A. The reaction mixture was chromatographed on a 50 × 880 mm Celite column in isooctane (240 ml), toluene (60 ml), and formamide (20 ml). Fractions (10 ml) were collected at intervals of 10 min. At fractions 510 and 795, the mobile phases were changed to isooctane (100 ml), toluene 50 ml), and isooctane (75 ml), toluene (150 ml), respectively. The bisteroidal carbonate **17a** emerged in a broad band from fractions 591–900. Crystallization from benzene afforded prismatic needles which slowly lost weight on drying *in vacuo* at

(15) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

room temperature. The product was dried to constant weight (922 mg, 88%) *in vacuo* at 65° over phosphoric anhydride: mp 170–174° and 272–275°; $[\alpha]_{365}$ 582°; $[\alpha]_D$ 127°; $\lambda_{max}$ 238 mμ (ε 32,100); $\nu_{max}$ 1235, 1160, and 1002 (17,20α-acetonide), 1754, 1275, and 790 cm$^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{49}H_{68}O_{11}$: C, 70.82; H, 8.00. Found: C, 70.57; H, 7.95.

**Bis(17,20β-isopropylidenedioxy-3,11-dioxopregn-4-en-21-yl) Carbonate (17b) from 16b.**—Phosgenation of 17,20β-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione[8] (1010 mg, 2.5 mmol) and chromatography of the reaction mixture in isooctane (200 ml), toluene (100 ml), and formamide (20 ml) on the same column used in the preparation of **17a** furnished 930 mg (89%) of **17b** as long needles from benzene–isooctane: mp 179–183° and 263–266°; $[\alpha]_{365}$ 690°; $[\alpha]_D$ 174°; $\lambda_{max}$ 238 mμ (ε 30,500); $\nu_{max}$ 1250, 1160, and 1002 (17,20β-acetonide), 1755, 1275, and 795 cm$^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{49}H_{66}O_{11}\cdot H_2O$: C, 69.31; H, 8.07. Found: C, 69.41; H, 8.06.

**Phosgenation of Cortisone (18) under Condition B.**—The reaction mixture from 360 mg (1 mmol) of cortisone afforded a fine reddish precipitate from methylene chloride. After charcoaling in ethyl acetate–methylene chloride and recrystallization, 36 mg of colorless needles were obtained, mp 281–283°. The ir spectrum was identical with that of a reference sample of 21-chloro-17-hydroxypregn-4-ene-3,11,20-trione[9] (**20**). Repeated crystallizations from the mother liquor in ethyl acetate and ethyl acetate–methylene chloride with selective charcoaling afforded 17,21-cyclocarbonyldioxypregn-4-ene-3,11,20-trione (**21**) as prisms (137 mg, 36%), mp 224–225°. Although the cyclic carbonate **21** was homogeneous by tlc, it was also obtained in a higher melting form (mp 270–272°) in those experiments which required column chromatography: $[\alpha]_{365}$ 725°; $[\alpha]_D$ 153°; $\lambda_{max}$ 238 mμ (ε 16,050); $\nu_{max}$ 1775 and 1110 (17,21-cyclic carbonate), 1740 cm$^{-1}$ (20-ketone).

*Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.41; H, 6.81.

**21-*O*-Carbomethoxy-17-hydroxypregn-4-ene-3,11,20-trione (19) from 18.**—To 100 mg of cortisone in cold pyridine (1 ml) was added 0.075 ml of methyl chlorocarbonate. After 1 hr at room temperature the product was recovered and crystallized from methanol as needles (94 mg, mp 224–225°; 9 mg, mp 221–223°) in a yield of 89%: $[\alpha]_{365}$ 1115°; $[\alpha]_D$ 238°; $\lambda_{max}$ 238 mμ (ε 15,700); $\nu_{max}$ 1765, 1285, and 797 cm$^{-1}$ (camylate).

*Anal.* Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23; $CH_3O$, 7.42. Found: C, 65.92; H, 7.25; $CH_3O$, 7.60.

**17,20α-Cyclocarbonyldioxy-20β-methoxy-21-hydroxypregn-4-ene-3,11-dione (22) and 19 from 21.**—A solution of 17,21-cyclocarbonyldioxypregn-4-ene-3,11,20-trione (600 mg) in methanol (50 ml) was refluxed for 19 hr. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (3:2) showed the complete conversion of starting material ($R_f$ 0.29) to roughly equal amounts of two products ($R_f$ 0.20 and 0.14). The mixture was chromatographed on a 30 × 830 mm silica gel column in ethyl acetate–isooctane (3:1), collecting 10-ml fractions every 10 min. Fractions 71–115 afforded 350 mg (54%) of needles from methanol, mp 225–226°. The ir spectrum was identical with that of the 21-camylate **19**, prepared by reaction of cortisone with methyl chlorocarbonate. Crystallization of fractions 131–210 from methanol furnished the methoxy cyclic carbonate **22** as prisms (111 mg, mp 258–261°; 15 mg, mp 251–253°) in a yield of 19%: $[\alpha]_{365}$ 451°; $[\alpha]_D$ 90°; $\lambda_{max}$ 238 mμ (ε 16,650); $\nu_{max}$ 1810 and 788 cm$^{-1}$ (cyclic carbonate); nmr δ 9.05 (s, 3, 18-$CH_3$), 8.58 (s, 3, 19-$CH_3$), 7.31 (s, 2, 12-$CH_2$), 6.52 (s, 3, $CH_3O$), 6.15, 5.92 (d, d, $J$ = 9.0 and 5.0 Hz, 21-$CH_2$).

*Anal.* Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23; $CH_3O$, 7.41. Found: C, 66.11; H, 7.34; $CH_3O$, 7.72.

Treatment of **22** (25 mg) with 0.05 ml each of acetic anhydride and pyridine for 3 hr at room temperature and crystallization from methanol gave 20 mg of 17,20α-cyclocarbonyldioxy-20β-methoxy-21-acetoxypregn-4-ene-3,11-dione (**23**) as rosettes: mp 213–213.5°; $[\alpha]_{365}$ 406°; $[\alpha]_D$ 84.7°; $\lambda_{max}$ 238 mμ (ε 16,150); $\nu_{max}$ 1818 and 782 (cyclic carbonate), 1759 and 1233 cm$^{-1}$ (acetoxyl); nmr δ 9.07 (s, 3, 18-$CH_3$), 8.59 (s, 3, 19-$CH_3$), 7.90 (s, 3, $CH_3CO$), 7.37, 7.25 (d, 2, $J$ = 16 Hz, 12-$CH_2$), 6.55 (s, 3, $CH_3O$), 5.76, 5.34 (d, 2, $J$ = 13.0 Hz, 21-$CH_2$).

*Anal.* Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01; $CH_3CO$, 9.35; $CH_3O$, 6.74. Found: C, 65.44; H, 7.51; $CH_3CO$, 8.92; $CH_3O$, 5.81.

**17,20α-Cyclocarbonyldioxy-20β-methoxy-3,11-dioxopregn-4-en-21-oic Acid (24) from 22.**—To a solution of 17,20α-cyclocarbonyldioxy-20β-methoxy-21-hydroxypregn-4-ene-3,11-dione (21 mg, 50 μmol) in acetic acid (0.95 ml) was added 15 mg (150 μmol) of chromic anhydride in water (0.05 ml). After 65 hr at 5° the solvent was evaporated and the residue was partitioned between methylene chloride and 2% sodium bicarbonate solution. The neutral fraction (2.6 mg) was not examined. From the acidic fraction (14.2 mg) were obtained prisms from methanol: mp 277–279°; $[\alpha]_{365}$ 464°; $[\alpha]_D$ 104°; $\lambda_{max}$ 238 mμ (ε 15,700); $\nu_{max}$ 1820 and 773 cm$^{-1}$ (cyclic carbonate).

*Anal.* Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 64.05; H, 6.62.

Treatment of **24** with excess ethereal diazomethane and crystallization of the product from methanol furnished methyl 17,20α-cyclocarbonyldioxy-20β-methoxy-3,11-dioxopregn-4-en-21-oate (**25**) as leaflets: mp 218–219°; $[\alpha]_{365}$ 474°; $[\alpha]_D$ 114°; $\lambda_{max}$ 238 mμ (ε 15,500); $\nu_{max}$ 1825 and 786 (cyclic carbonate), 1755 cm$^{-1}$ (carbomethoxyl).

*Anal.* Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77; $CH_3O$, 13.90. Found: C, 64.47; H, 6.86; $CH_3O$, 13.53.

**17,21-Cyclocarbonyldioxypregn-4-ene-3,11-dione (27) from 26.**—Phosgenation of 17,21-dihydroxypregn-4-ene-3,11-dione[12] (104 mg) under condition B was followed by chromatography of the reaction mixture on a 15 × 500 mm silica gel column in ethyl acetate–isooctane (4:1), collecting 2-ml fractions per 10 min. The pooled contents of fractions 191–420 crystallized from methanol as prismatic needles (89 mg, mp 254.5–255°; 6 mg, mp 256–257.5°) in a yield of 85%: $[\alpha]_{365}$ 600°; $[\alpha]_D$ 140°; $\lambda_{max}$ 238 mμ (ε 16,200); $\nu_{max}$ 1745 and 1115 cm$^{-1}$ (17,21-cyclic carbonate).

*Anal.* Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.80; H, 7.62.

Treatment of **27** (20 mg) in methanol (2 ml) with 0.5% methanolic potassium bicarbonate (2 ml) for 21 hr at room temperature afforded 10.6 mg of prisms from acetone, mp 186.5–188.5°. A mixture melting point with 20-deoxycortisone **26** was 187–189° and their ir spectra were identical.

**Bis(17-hydroxy-3,11-dioxopregn-4-en-21-yl) Carbonate (28) and 27 from 26.**—Phosgenation of **26** (104 mg) under condition A was followed by chromatography on a 15 × 500 mm Celite column in toluene–formamide, collecting fractions of 2 ml each 10 min. From fractions 81–125 was obtained 68 mg (61%) of cyclic carbonate **27**, mp 254.5–256.5°. The residue (17.5 mg) from fractions 151–220 afforded the bisteroidal carbonate **28** as prismatic needles from methanol (13.4 mg, mp 240–241°): $[\alpha]_{365}$ 740°; $[\alpha]_D$ 165°; $\lambda_{max}$ 238 mμ (ε 31,000); $\nu_{max}$ 3510 (hydroxyl), 1749, 1275, and 785 cm$^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{43}H_{58}O_9$: C, 71.84; H, 8.13. Found: C, 71.83; H, 8.24.

**17,21-Cyclocarbonyldioxypregn-5-ene-3,20-dione 3,20-Bis(ethylene Ketal) (31) from 29.**—The product from reaction of 17,21-dihydroxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal)[13] (434 mg, 1 mmol) under condition B crystallized as platelets from methanol (405 mg, mp 232–235°; 35 mg, mp 228–231°) in a yield of 96%: $[\alpha]_{365}$ −152°; $[\alpha]_D$ −48°; $\nu_{max}$ 1755 and 1110 cm$^{-1}$ (17,21-cyclic carbonate).

*Anal.* Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.82; H, 7.79.

**17,21-Cyclocarbonyldioxypregn-4-ene-3,20-dione 20-Ethylene Ketal (33) from 31.**—To a solution of 17,21-cyclocarbonyldioxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal) (50 mg) in a mixture of methylene chloride (2 ml) and acetone (38 ml) was added *p*-TSA (10 mg). After 20 hr at room temperature the product was recovered and crystallized from methanol as leaflets (40 mg, mp 231–232°) in a yield of 88%: $[\alpha]_{365}$ −8.2°; $[\alpha]_D$ 65.5°; $\lambda_{max}$ 240 mμ (ε 16,600); $\nu_{max}$ 1753 and 1112 cm$^{-1}$ (17,21-cyclic carbonate).

*Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.40; H, 7.86.

**Bis(17-hydroxy-3,20-bisethylenedioxypregn-5-en-21-yl) Carbonate (35) and 33 from 29.**—Phosgenation of 17,21-dihydroxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal) (87 mg) was carried out under condition A. The reaction mixture was chromatographed on a 20 × 730 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 5 ml per 10 min. The contents of fractions 41–160 crystallized from methanol, giving the bisteroidal carbonate **35** as platelets (32 mg, mp 283–285°) in a yield of 35%: $[\alpha]_{365}$ −109°; $[\alpha]_D$ −36.4°; $\nu_{max}$ 3520 (hydroxyl), 1755, 1265, and 790 cm$^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{51}H_{74}O_{13}$: C, 68.43; H, 8.33. Found: C, 68.58; H, 8.16.

Further processing of the mother liquor from **35** gave the cyclic carbonate **31** in a total yield of 30 mg (33%), mp 235–238°. Continued development of the column with ethyl acetate–isooctane (4:1) provided 11 mg of starting material (**29**) mp 212–214°.

**17,21-Cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-Bis(ethylene Ketal) (32) from 30.**—Phosgenation of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal)[14] (448 mg, 1 mmol) was effected using condition B. Crystallization of the product from methanol gave platelets (385 mg, mp 286–288°; 70 mg, mp 278–281°) in a yield of 96%: $[\alpha]_{365}$ −23.2°; $[\alpha]_D$ −31.3°; $\nu_{max}$ 1755 and 1110 cm$^{-1}$ (17,21-cyclic carbonate).

*Anal.* Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.99; H, 7.27.

**17,21-Cyclocarbonyldioxypregn-4-ene-3,11,20-trione 20-Ethylene Ketal (34) from 32.**—Treatment of 17,21-cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (50 mg) with *p*-TSA in methylene chloride–acetone was carried out as in the preparation of **33** from **31**. The product crystallized from methanol as needles (37 mg, mp 259–261°) in a yield of 82%: $[\alpha]_{365}$ 553°; $[\alpha]_D$ 131°; $\lambda_{max}$ 238 mμ (ε 15,300); $\nu_{max}$ 1755 and 1115 cm$^{-1}$ (17,21-cyclic carbonate).

*Anal.* Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.05; H, 7.11.

**Bis(17-hydroxy-3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) Carbonate (36) and 32 from 30.**—The reaction mixture from phosgenation under condition A of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (90 mg) was chromatographed on a 20 × 730 mm silica gel column in ethyl acetate–isooctane (3:2). After emergence of fraction 300 the system was changed to ethyl acetate–isooctane (4:1). Fractions (5 ml) were collected every 10 min. Fractions 171–280 contained the 17,21-cyclic carbonate **32**. Crystallization from methanol gave 38 mg (40%) of platelets, mp 285–286°. Crystallization of the residue from fractions 311–400 gave the bisteroidal carbonate **26** as needles (34 mg, 37%): mp 254–257°; $[\alpha]_{365}$ 91.8°, $[\alpha]_D$ −0.94°; $\nu_{max}$ 1760, 1265, and 787 cm$^{-1}$ (bisteroidal carbonate).

*Anal.* Calcd for $C_{51}H_{70}O_{15}$: C, 66.36; H, 7.64. Found: C, 66.47; H, 7.48.

**Registry No.**—**1**, 36674-99-4; **2**, 36623-73-1; **3**, 36623-74-2; **4**, 36623-75-3; **5**, 36623-76-4; **6**, 36675-00-0; **7**, 36623-11-7; **8**, 36623-12-8; **9**, 36675-01-1; **10**, 36623-13-9; **11**, 36623-14-0; **12**, 36623-15-1; **13**, 36623-16-2; **14**, 36623-17-3; **15**, 36623-18-4; **17a**, 36623-19-5; **17b**, 36623-20-8; **19**, 36623-21-9; **21**, 36623-22-0; **22**, 36623-23-1; **23**, 36623-24-2; **24**, 36623-25-3; **25**, 36623-26-4; **27**, 36623-27-5; **28**, 36623-28-6; **31**, 36675-02-2; **32**, 36623-29-7; **33**, 36623-30-0; **34**, 36623-31-1; **35**, 36675-03-3; **36**, 36623-32-2; phosgene, 75-44-5.

**Acknowledgment.**—The author is obliged to Dr. John H. Schneider for his generous assistance throughout the course of this work.

# Nucleosides. LXXVI. A Synthesis of a Carbon–Carbon Bridged Pyrimidine Cyclonucleoside[1]

JAIME A. RABI AND JACK J. FOX*

*Division of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021*

*Received June 14, 1972*

The synthesis of a pyrimidine cyclonucleoside containing a carbon to carbon linkage between C-6 and C-5′ has been achieved. Oxidation of 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**2**) with DMSO–DCC gave the corresponding 5′ aldehyde isolated as its 1,3-diphenylimidazolidine derivative **3**. Hydrolysis of the ester **3** gave the 5-hydroxy derivative **4**, which upon treatment with Dowex-50 ($H^+$) in aqueous THF afforded the 5′ aldehyde of 2′,3′-*O*-isopropylidene-5-hydroxyuridine (**5**). Base-catalyzed intramolecular hydroxyalkylation of **5** proceeded stereoselectively to give cyclonucleoside **6**, which on treatment with acid yielded the free cyclonucleoside **6a**. Formation of **6** from **5**, facilitated by the presence of the isopropylidene group, is thought to proceed by addition of the C-6 anion to the 5′ aldehyde group. Experimental evidence supporting this mechanism is discussed.

Cyclonucleosides containing a bond from a ribose carbon to a purine or pyrimidine carbon were first reported by Hogenkamp[2] and by Johnson and coworkers.[3] Thus aerobic photolytic cleavage of coenzyme $B_{12}$ gave, among other products, the so-called Nucleoside A. The latter nucleoside was identical with the product obtained by anaerobic photolysis of coenzyme $B_{12}$ and it was tentatively identified as 8,5′-cycloadenosine.[2] Likewise, photolysis of 5′-deoxyinosylcobalamin gave the cyclic nucleoside of hypoxanthine.[3a] In contrast to these results, the anaerobic photolysis of 5′-deoxy-2′,3′-*O*-isopropylideneuridinylcobalamin gave hydroxycobalamin and a crystalline nucleoside which was tentatively identified as 2′,3′-*O*-isopropylidene-6,5′-cyclo-5,6-dihydrouridine.[3b] On the other hand, Keck and Hagen[4] reported the formation of 8,5′-cycloadenylic acid by irradiation of adenylic acid. Presumably all of these reactions involve free-radical mechanisms. Of related interest is the reported synthesis[5] of 2,2′-methylene cyclonucleosides by the photolysis of pyrimidine nucleoside oxosulfonium ylides. More recently Harper and Hampton[6] reported that treatment of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid with methyllithium in tetrahydrofuran gave a complex mixture of products from which 2′,3′-*O*-isopropylidene-5′-keto-8,5′-cycloadenosine was isolated in ~5% yield. This latter nucleoside was reduced with sodium borohydride to 2′,3′-*O*-isopropylidene-8,5′-cycloadenosine.[6]

Since hydroxymethylation of 5-hydroxy-1-methyluracil had been shown to proceed readily to yield 5-

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748), and a Postdoctoral Fellowship (J. A. R.) from the Gimbel Foundation.

(2) H. P. C. Hogenkamp, *J. Biol. Chem.*, **238**, 477 (1963).

(3) (a) A. W. Johnson, L. Mervyn, N. Shaw, and E. L. Smith, *J. Chem. Soc.* 4146 (1963); (b) A. W. Johnson, D. Oldfield, R. Rodrigo, and N. Shaw, *ibid.* 4080 (1964).

(4) K. Keck and U. Hagen, *Naturwissenschaften*, **53**, 304 (1966); E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **8**, 578 (1969).

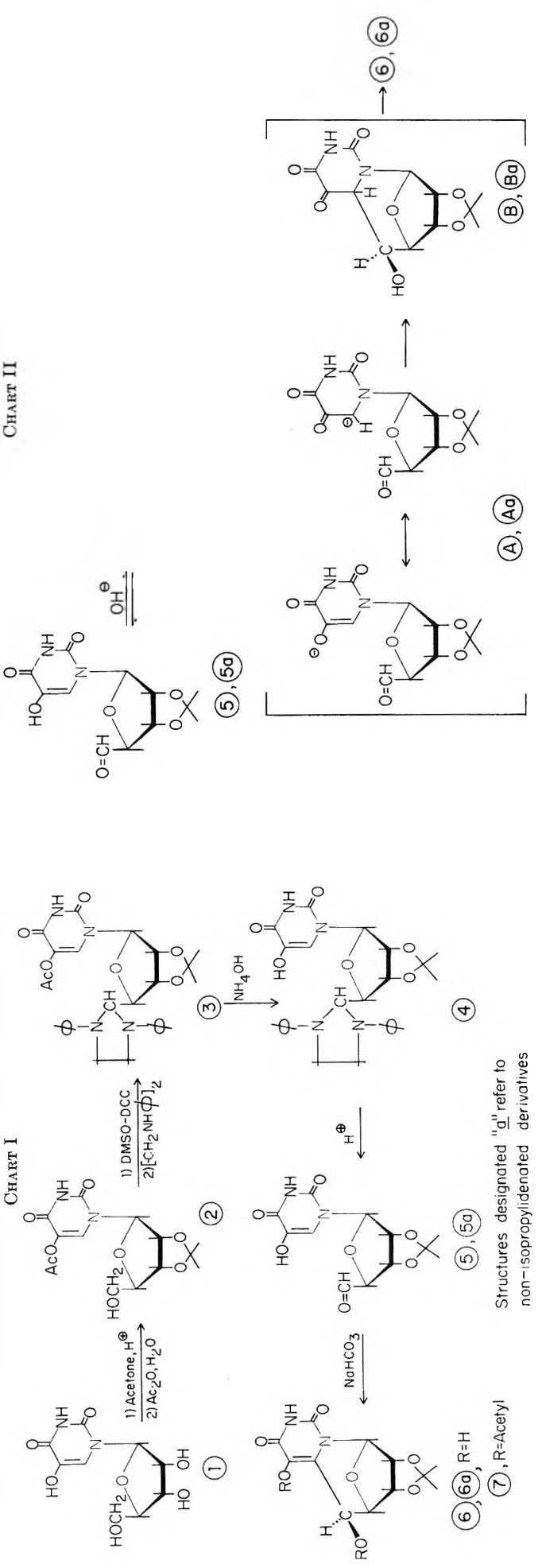
(5) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **91**, 7752 (1969).

(6) P. J. Harper and A. Hampton, *J. Org. Chem.*, **37**, 795 (1972).

hydroxy-6-hydroxymethyl-1-methyluracil,[7] we envisioned that the synthesis of a 6,5′ cyclonucleoside could be achieved by intramolecular hydroxyalkylation of the 5′ aldehyde of 5-hydroxyuridine (**5a**). (5-Hydroxyuridine is a naturally occurring component of certain yeast RNAs.)[8] This paper describes the synthesis of **5a** and its ketal **5** and their conversion into their corresponding 6,5′ cyclonucleosides **6a** and **6** as part of our program to prepare 6-substituted pyrimidine nucleosides of potential biochemical interest.

Isopropylidination of 5-hydroxyuridine (**1**, Chart I) in acetone containing 2,2-dimethoxypropane[9] followed by acetylation in aqueous medium gave 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**2**). Oxidation of **2** with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of pyridinium trifluoroacetate[10] gave the 5′ aldehyde of **2**, which was isolated as its crystalline 1,3-diphenylimidazolidine derivative **3** upon reaction with *N*,*N*′-diphenylethylenediamine.[11] Treatment of **3** with ethanolic ammonia gave the free 5-hydroxy derivative **4**, which on treatment with Dowex 50 ($H^+$) in 70% tetrahydrofuran–water[12] gave the free aldehyde **5**. A facile conversion to the cyclonucleoside **6** (or **6a**) was observed when **5** (or **5a**) was treated with 1 equiv of sodium bicarbonate in aqueous medium. The structure of **6** was demonstrated on the basis of the following evidence: elemental analysis was consistent with the empirical formula; the ultraviolet absorption characteristics were very similar to those reported for 5-hydroxy-6-alkylpyrimidines;[7] the pmr spectrum of **6a** in dimethyl sulfoxide-$d_6$ showed the lack of H-6 absorption and the anomeric proton signal was a singlet, a good indication of cyclo- (or anhydro-) nucleoside linkage involving C-5′.[3b,6,13] Three exchangeable protons were detected upon addition of deuterium oxide. Furthermore, nucleoside **6** showed *well-resolved* signals for H-4′ and H-5′ as a pair of doublets at $\delta$ 4.47 and $\delta$ 4.97, respectively, with a coupling constant of $J_{4',5'} = 7.5$ Hz. These results are in contrast to the pmr data reported by Harper and Hampton[6] for 2′,3′-*O*-isopropylidene-8,5′-cycloadenosine, which showed poorly resolved signals for H-4′ and H-5′ attributable to a mixture of diastereoisomers in their product. Acetylation of **6** with excess acetic anhydride in pyridine gave the diacetate **7**. In the latter compound H-5′ appeared at $\delta$ 6.03 and was coupled to H-4′, which appeared as a doublet at $\delta$ 4.65 ($J_{4',5'} = 7.5$ Hz), thus confirming the previous assignments.

Theoretically, the intramolecular hydroxyalkylation of **5** could lead to two diastereoisomers. However, inspection of Dreiding models of the two possible isomers shows that the large coupling constant ($J_{4',5'} = 7.5$ Hz) could be rationalized *only* in terms of the isomer having the *S* configuration at C-5′ as depicted in structure **6**. (The $J_{4',5'}$ value for the *R* isomer should be much smaller since the dihedral angle in that case is almost 90°.) The pmr spectrum of a reaction mix-




(7) B. A. Otter, A. Taube, and J. J. Fox, *J. Org. Chem.*, **36**, 1251 (1971).
(8) A. W. Lis and W. E. Passarge, *Arch. Biochem. Biophys.*, **114**, 593 (1966).
(9) A. Hampton, *J. Amer. Chem. Soc.*, **83**, 3640 (1961).
(10) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661, 5670 (1965).
(11) W. J. Gottstein, G. E. Bocian, L. B. Crast, K. Dadabo, J. M. Essery, J. C. Godfrey, and L. C. Cheney, *J. Org. Chem.*, **31**, 1922 (1966).
(12) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).
(13) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).

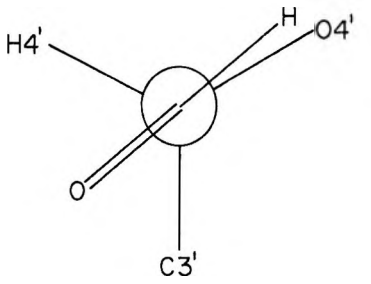



Figure 1.—Newman projection of a portion of **5** or **5a** showing C-4′–C-5′ viewed from C-5′.

ture containing nucleoside **6** was almost identical with that of isolated **6**, indicating that isomer **6** is the main—if not the exclusive—product. This remarkable stereoselectivity in the formation of **6** from **5** may be explained by consideration of the factors which determine the rotamer population around C-4′ and C-5′. The most favorable conformation would be that in which the carbonyl oxygen is farthest removed from the pyrimidine ring and sugar ring oxygen, as shown in Figure 1. In such a conformation, the 5′ carbonyl is flanked by H-4′ and C-3′. Attack by the C-6 anion[14] (*vide infra*) on the 5′ aldehyde would then be expected to give mainly—or solely—**6**.

At the outset of this work we expected that the intramolecular hydroxyalkylation at C-6 by the 5′-aldehyde group would be promoted by the presence of the isopropylidene group.[15] The following results give support to this expectation. An aqueous solution of **5** ($\sim 2 \times 10^{-4}$ *M*) lost ~75% of its selective absorption at 280 nm over a period of ~10 min, after which time a new peak at 286 nm slowly emerged and reached a maximum value in ~1.5 hr. The absorption of this latter peak is that of **6**. This sequence of events was not observed when the pH of the solution containing **5** was kept below 3.5. However, the appearance of the maximum at 286 nm could not be prevented by acidifying the solution of **5**, which had lost 75% of its selective absorption at 280 nm. In sharp contrast to these observations, it was found that an aqueous solution of **5a** did not undergo any appreciable change for as long as 1 hr. Instead its absorption maximum slowly shifted from ~280 nm toward ~285 nm, indicating that **6a** was being formed. This latter transformation took place however in ~6 days at room temperature. In contrast, formation of **6a** was immediately observed when a solution of **5a** was treated with dilute sodium hydroxide (pH ~10–11). That **6a** was the product formed was proved by synthesis from **5a**. It could then be shown that **6a** was identical with the product obtained by treating **6** with acid.

Formation of **6** (or **6a**) from **5** (or **5a**) probably proceeds through the formation of the mesomeric anion A[14,16] (or Aa) (Chart II). Nucleophilic attack of C-6 anion on the 5′-carbonyl group would yield intermediate B (or Ba) which could tautomerize to yield cyclonucleoside **6** (or **6a**). Clearly, this mechanism is supported by the observations made in the transformation of **5** to **6** in dilute aqueous solution: first, when the ionization of the 5-OH group in **5** was prevented by addition of acid no change was noticed, indicating that anion A could not be formed; secondly, the loss of uv absorption is a good indication that intermediate B is formed. In the case of **5**, formation of B is facilitated by the presence of the isopropylidene group.[15] Formation of B from **5** is fast compared with the rate of formation of **6** from B; therefore accumulation (loss of uv) of B is noticed. In contrast, **5a** does not lose uv absorption (Ba is not accumulated) but slowly yields **6a**. In this latter case the rate of formation of **6a** from Ba is faster than the formation of Ba from **5a**.

(14) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(15) For a discussion of this effect see ref 13 and references therein. More recent references to this effect: Y. Kondo, J. L. Fourrey, and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3527 (1971); K. Isono and T. Azuma, *Chem. Pharm. Bull.*, **20**, 193 (1972).

(16) K. Ikeda and Y. Mizuno, *ibid.*, **19**, 564 (1971).

## Experimental Section

**General Procedures.**—Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The proton magnetic resonance spectra (pmr) were recorded on a Varian A-60 spectrometer using DMSO-$d_6$ as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in parts per million ($\delta$). Values for coupling constants (hertz) are first order. Pmr signals are s = singlet, d = doublet, m = multiplet, b = broad. Thin layer chromatography was performed on silica gel $GF_{254}$. Detection of various compounds on the plates was done under ultraviolet light, and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at 110°. Free 5-hydroxy derivatives were detected with a $FeCl_3$ spray and aldehydes with a phenylhydrazine spray. Evaporations were carried out *in vacuo* with bath temperature below 40°. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Uv spectra were recorded on a Unicam SP 500 spectrometer.

**5-Acetoxy-2′,3′-*O*-isopropylideneuridine (2).**—5-Hydroxyuridine[17] (10.4 g, 40 mmol) was suspended in a solution of *p*-toluenesulfonic acid (2.85 g, 15 mmol) in 300 ml of dry acetone containing 12 ml of 2,2-dimethoxypropane. After 1 hr, the rapidly stirred reaction mixture still contained some unreacted starting material as shown by tlc ($CHCl_3$–MeOH, 10:1). An additional 5 ml of 2,2-dimethoxypropane was added and the reaction was continued for an additional 1.5 hr. Tlc of the reaction mixture showed that most of the starting material had disappeared to give mainly the desired ketal ($R_f$ 0.50) and a small amount of a faster moving, unidentified product. The reaction mixture was then concentrated and the gummy residue was taken up in a solution of 1.4 g of $NaHCO_3$ in 200 ml of water. The resulting solution was stirred at room temperature and 5 ml of acetic anhydride was added at once. After a few minutes precipitation of the product started. The reaction mixture was then cooled and filtered. The product was washed with several portions of cold water and dried *in vacuo* at 70°, giving 10.3 g (76%) of **2**, mp 155–156°. The mother liquors were extracted with two 100-ml portions of ethyl acetate. The organic layer was dried over $MgSO_4$ and then evaporated. The white residue was recrystallized from water to yield 2 g of **2** (total yield 90%). Tlc examination of these two crops showed only one spot. A small amount of **2** was recrystallized from water to yield an analytical sample: mp 170–171°; pmr $\delta$ 7.97 (s, 1, H-6), 5.84 (d, 1, $J_{1',2'}$ = 2.3 Hz, H-1′), 4.83 (m, 2, H-2′ and H-3′), 4.11 (m, 1, H-4′), 3.58 (m, 2, H-5′s), 2.23 (s, 3, acetyl), 1.49 and 1.29 (s, 3 each, isopropylidene methyls); two exchangeable protons were detected by addition of $D_2O$ (NH and 5′-OH).

*Anal.* Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.99; H, 5.01; N, 8.03.

**1-[4(*R*)-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-5-acetoxyuracil (3).**—Compound **2** (6.84 g, 20 mmol) and 16 g of DCC were dissolved in 200 ml of DMSO. Pyridine (2 ml) and trifluoroacetic acid (1 ml) were than added and the resulting mixture was rapidly stirred at room temperature for 15 hr. Water (20 ml) was then added and the resulting mixture was stirred for an additional 30 min. Dicyclo-

(17) D. W. Visser in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 428.

hexylurea was removed by filtration and the clear yellowish solution was evaporated until most of the DMSO was eliminated. The product was dissolved in 200 ml of $CH_2Cl_2$ and filtered to eliminate some dicyclohexylurea still present. 1,2-Diphenylethylenediamine (4.24 g, 20 mmol) dissolved in 10 ml of ether was then added and the resulting mixture was refluxed for 45 min. An additional 2 mmol of the diamine was added and the reaction was continued for a total of 2 hr. The reaction mixture was cooled and extracted with water (3 × 30 ml). The organic layer was dried over magnesium sulfate and evaporated to a syrup, which was taken up in 150 ml of diethyl ether and refluxed for 15 min with continuous stirring. This partially dissolved the syrup and gave some finely divided precipitate. The mixture was allowed to cool and then stored overnight in the cold. The product was triturated and filtered to yield 7.0 g of compound **3**. A second crop was obtained (total yield 7.6 g, 71%). This material was recrystallized from absolute ethanol, filtered, washed with ether, and dried to give 6 g of pure **3**: mp 217–218°; pmr δ 7.52 (s, 1, H-6), 6.95 (m, 10, phenyls), 5.85 (m, 2, H-1′ and H-5′), 4.97 (bm, 2, H-2′ and H-3′), 4.33 (bm, 1, H-4′), 3.63 (b, 4, $-CH_2CH_2-$), 2.22 (s, 3, acetyl), 1.37 and 1.23 (2 s, 3 each, isopropylidene methyls). Upon addition of $D_2O$, one exchangeable proton could be detected.

*Anal.* Calcd for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66; N, 10.48. Found: C, 63.52; H, 5.68; N, 10.44.

**1-[4(*R*)-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-5-hydroxyuracil** (**4**).—Compound **3** (2.136 g, 4 mmol) was dissolved in 120 ml of boiling ethanol, and 8 ml of concentrated aqueous ammonia was added. The mixture was kept under reflux and after 10 min the product started to separate. After 30 min the condenser was removed and the heating was continued until all ammonia was eliminated. The reaction mixture was allowed to cool and then it was left at 4° for 16 hr. The product was removed by filtration and washed with cold ethanol and then with ether to afford 1.87 g (95%) of compound **4**. This product showed only one spot on tlc ($CHCl_3$–MeOH, 10:1): mp 232–233° dec; pmr δ 7.12 (s, 1, H-6), 6.97 (m, 10, phenyls), 5.83 (m, 2, H-1′ and H-5′), 4.98 (m, 2, H-2′ and H-3′), 4.28 (m, 1, H-4′), 3.63 (b, 4, $-CH_2CH_2-$), 1.40 and 1.23 (2 s, 3 each, isopropylidene methyls). Two exchangeable protons were detected on addition of $D_2O$ (5-OH and NH).

*Anal.* Calcd for $C_{26}H_{28}N_4O_6$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.69; H, 5.77; N, 11.33.

**1-(2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanosyl)-5-hydroxyuracil** (**5**).—Compound **4** (0.493 g, 1 mmol) was dissolved in 20 ml of tetrahydrofuran and 10 ml of water. Dowex 50 ($H^+$), 5 g, was then added in one portion and the reaction mixture was rapidly stirred at room temperature. After 40 min all the starting material ($R_f$ 0.58) had disappeared as shown by tlc ($CHCl_3$–MeOH, 10:1) and **5** was the only uv-absorbing product. However, if the plate was first sprayed with 10% $H_2SO_4$ and then heated, two new spots could be detected. These have not yet been identified but presumably are formed in solution by intramolecular interactions between the sugar and the aglycon moiety. The resin was filtered off and the filtrate was concentrated *in vacuo* to a white residue. The residue was suspended in chloroform and then it was filtered and dried *in vacuo* to give 0.273 g (91.5%) of the aldehyde **5**: mp 160–162° dec; uv max (0.1 *N* HCl) 280 nm; pmr δ 9.30 (s, 1, –CHO). On addition of $D_2O$ the absorption at δ 9.30 rapidly disappeared to give the hydrate: pmr (DMSO-$d_6$–$D_2O$) δ 7.38 (s, 1, H-6), 5.88 (d, 1, $J_{1',2'}$ = 2.8 Hz, H-1′), 4.93 (d, 1, $J_{4',5'}$ = 4.4 Hz, H-5′), 4.83 (m, 2, H-2′ and H-3′), 3.88 (dd, $J_{4',5'}$ = 4.4, $J_{3',4'}$ = 1.5 Hz, H-4′), 1.49 and 1.30 (pair of singlets, 3 each, isopropylidene methyls). Addition of $D_2O$ to the solution of **5** in DMSO-$d_6$ also allowed the detection of 1.5 mol of water.

*Anal.* Calcd for $C_{12}H_{14}N_2O_7 \cdot 1.5\ H_2O$: C, 44.31; H, 5.23; N, 8.62. Found: C, 44.41; H, 4.90; N, 8.82.

**1-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)-5-hydroxyuracil** (**5a**).—The product obtained from the treatment of 1 mmol of **4** with Dowex 50 ($H^+$) was dissolved in a mixture of 2 ml of trifluoroacetic acid and 0.5 ml of water.[18] As the reaction proceeded, **5a** started to separate and after 10 min the solvents were removed *in vacuo*. The residue was dissolved in water and the solution was concentrated again. The residue was suspended in acetone and filtered to give 0.2 g (77%) of aldehyde **5a**, uv max (0.1 *N* HCl) 280 nm. A 35-mg portion of this product was dissolved in $D_2O$ and then concentrated *in vacuo*. This operation was repeated twice. The residue was dissolved in $D_2O$ and the pmr was obtained (TMS as external standard): δ 7.50 (s, 1, H-6), 5.97 (m, 1, H-1′), 5.20 (d, 1, $J_{4',5'}$ = 3.8 Hz, H-5′), 4.78 (s, DOH), 4.33 (m, 2, H-2′ and H-3′), 4.02 (dd, 1, $J_{4',5'}$ = 3.8 Hz, H-4′).

**2′,3′-*O*-Isopropylidene-6,5′(*S*)-cyclo-5-hydroxyuridine** (**6**).—Compound **4** (1.97 g, 4 mmol) was dissolved in 100 ml of 70% aqueous tetrahydrofuran. To the well-stirred solution 20 g of Dowex 50 ($H^+$) were added at once and the reaction was kept at room temperature for 1.5 hr. During this step some deisopropylidenation was observed as detected by tlc. The resin was filtered off and the filtrate was treated with 0.335 g of $NaHCO_3$. After 15 min the solution ($\lambda_{max}^{pH\ 1}$ 286) was neutralized with Dowex 50 ($H^+$) and evaporated to dryness, yield 1.02 g. Pmr of this material showed it to be a mixture of **6** (82%) and **6a** (18%). The combined yield was 87%. This material was twice recrystallized from ethanol to yield pure **6**: mp 242–244° dec; uv max (0.1 *N* HCl) 286 nm (ε 9540), uv min (0.1 *N* HCl) 248 nm (ε 1870), shoulder ~225 nm, uv max (pH 10) 313, 243 nm (ε 8040, 6100), uv min (pH 10) 273.5 nm (ε 2900); uv max (0.1 *N* NaOH) 309 nm, shoulder at 245 nm, uv min (0.1 *N* NaOH) 271.5 nm (ε 2605); pmr δ 5.83 (s, 1, H-1′), 5.12 (d, 1, $J_{2',3'}$ = 5.5 Hz, H-2′), 4.97 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-5′), 4.68 (d, 1, $J_{2',3'}$ = 5.5 Hz, H-3′), 4.47 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-4′), 1.40 and 1.27 (2 s, 3 each, isopropylidene methyls). On addition of $D_2O$, three protons were exchanged (NH, 5-OH, and 5′-OH).

*Anal.* Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39. Found: C, 48.52; H, 4.94; N, 9.32.

**6,5′(*S*)-Cyclo-5-hydroxyuridine** (**6a**).—A portion of the above mixture containing **6** (0.45 g) was dissolved in 10 ml of 80% acetic acid. The reaction mixture was then heated under reflux and the progress of the hydrolysis was followed by tlc using $CH_2Cl_2$–MeOH (5:1) as solvent. After 3 hr, most of **6** ($R_f$ 0.71) disappeared. The solvent was removed *in vacuo* and the residue was taken up in 25 ml of hot ethanol. Enough water was added to dissolve the solid and the solution was filtered and allowed to cool. After standing for 15 hr at 4° the crystalline product was filtered, washed with ethanol and ether, and dried to give 0.31 g (78%) of cyclonucleoside **6a**. Recrystallization from water gave an analytical sample: mp 215–217° dec; pmr δ 11.48 (b, 1, NH), 8.67 (b, 1, 5-OH), 5.72 (s, 1, H-1′), 5.21 (b, d, 1, $J_{5',5'\text{-OH}} \cong 5$ Hz, 5′-OH), 4.92 (b d, 1, $J_{5',5'\text{-OH}} \simeq 5$, $J_{4',5'}$ = 7 Hz, H-5′), 4.53 (b d, 1, $J_{2',3'}$ = 6 Hz, H-2′), 4.28 (d, 1, $J_{4',5'}$ = 7 Hz, H-4′), 4.02 (b d, 1, $J_{2',3'}$ = 6 Hz, H-3′), 3.42 (b, 2, 2′-OH and 3′-OH). Addition of $D_2O$ exchanged the signals at δ 11.48, 8.67, 5.21, and 3.42 and the broad doublets became sharper.

*Anal.* Calcd for $C_9H_{10}N_2O_7$: C, 41.87; H, 3.90; N, 10.85. Found: C, 41.73; H, 3.91; N, 10.77.

**6,5′(*S*)-Cyclo-5-hydroxyuridine** (**6a**) **from 5a**.—Compound **5a** (0.1 g, 0.38 mmol) was dissolved in 10 ml of water, and 40 mg of $NaHCO_3$ was added. After ~2 hr, the uv maximum shifted from 280 nm to ~285 nm and remained constant thereafter. The mixture was adjusted to pH 5 with Dowex 50 ($H^+$) and the resulting mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in ~2 ml of hot water. On cooling, 40 mg of **6a** crystallized, mp 215–217°. Its pmr spectrum was identical with that of **6a** obtained from **6** by acid hydrolysis.

**5-Acetoxy-5′-acetyl-2′,3′-*O*-isopropylidene-6,5′(*S*)-cyclouridine** (**7**).—Compound **6** (0.149 g, 0.5 mmol) was dissolved in 10 ml of pyridine, and 2 ml of acetic anhydride was added. The resulting mixture was allowed to stand at room temperature for 36 hr. The solvent was evaporated and the residue was dissolved in ethanol and evaporated again. This last procedure was repeated twice. Finally the glassy residue was dissolved in ~0.5 ml of ethanol, and water was added to precipitate the product. The mixture was left at 4° overnight and the precipitate was collected, washed with water, and dried to give 0.145 g (76%) of the diacetate **7**: mp 228.5–229.5°; pmr δ 6.03 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-5′), 5.96 (s, 1, H-1′), 4.96 (m, 2, H-2′ and H-3′), 4.65 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-4′), 2.15 (s, 6, 5-acetoxy and 5′-acetyl), 1.42 and 1.30 (pair of singlets, 3 each, isopropylidene methyls). One exchangeable proton (NH) could be detected by addition of $D_2O$.

*Anal.* Calcd for $C_{15}H_{18}N_2O_9$: C, 50.27; H, 4.75; N, 7.33. Found: C, 50.44; H, 4.71; N, 7.36.

**Registry No.**—**2**, 36507-00-3; **3**, 36507-01-4; **4**, 36507-02-5; **5**, 36507-03-6; **5a**, 36507-04-7; **6**, 36507-05-8; **6a**, 36507-06-9; **7**, 36507-07-0.

(18) J. E. Christensen and L. Goodman, *Carbohyd. Res.*, **7**, 510 (1968).

# Synthesis of the 335-nm Photoproduct of Cytosine and 4-Thiouracil

DONALD E. BERGSTROM, ICHIZO INOUE, AND NELSON J. LEONARD*

*The School of Chemical Sciences, The University of Illinois, Urbana, Illinois 61801*

*Received May 31, 1972*

Application of the Vilsmeier formylation reaction to 4-methylpyrimidin-2-one (4) followed by treatment with hydroxylamine gave 4-(isoxazol-4-yl)pyrimidin-2-one (5), which was transformed to 4-(α-formylcyanomethyl)-pyrimidin-2-one (6) by rearrangement with alkali in 53% overall yield (from 4). Methylation of 6 with NaH and MeI in dimethylformamide gave 4-(α-formylcyanomethyl)-1-methylpyrimidin-2-one (2) in 76% yield. Ethylation of 6 with triethyl orthoformate afforded a mixture of 4-(α-ethoxymethylenecyanomethyl)-2-ethoxypyrimidine (9) and 1-ethyl-4-(α-formylcyanomethyl)pyrimidin-2-one (8). The positions of alkylation in compounds 2 and 8 were established by nuclear Overhauser effect measurements. 5-(4-Pyrimidin-2-one)cytosine (7a), was obtained in low yield on fusion of the diethylated compound 9 or the cyanoaldehyde 6 lithium salt with urea, a subsequent acid hydrolysis being required with the former compound. A similar reaction with thiourea produced 5-(4-pyrimidin-2-one)-2-thiocytosine (7b). The synthesis of 5-(4-pyrimidin-2-one)cytosine (7a), identical with the product of irradiation of cytosine and 4-thiouracil at 335 nm, provides direct proof of the structure of this moiety as it is formed in *Escherichia coli* tRNAs by the photolinking of 4-thiouridine (base no. 8) and cytidine (base no. 13) under long wavelength ultraviolet irradiation.

Since it was found[1-3] that irradiation of several *Escherichia coli* tRNAs at 335 nm brings about covalent bond formation between the 4-thiouridine in position 8 and the cytidine in position 13 from the 5′-terminal end, the determination of the mode of the linkage has been of great importance in providing detailed information concerning the tertiary structure of the tRNAs. We have recently identified the binucleoside tRNA photoproduct as 5-(1-β-D-ribofuranosyl-4-pyrimidin-2-one)cytidine.[4] The corresponding bipyrimidine product, 5-(4-pyrimidin-2-one)cytosine, Pyo(4-5)Cyt[5] (**7a**), is obtained on irradiation (335 nm) of an aqueous solution of 4-thiouracil and cytosine at 4°.[6] Rhoades and Wang[7,8] have also reported formation of the same compound **7a** on irradiation (254 nm) of polycytidylic acid in aqueous solution (pH 4–7) followed by acid hydrolysis. We have further shown that identification of the single structure **7a** is sufficient to fix *one-third of the total tRNA tertiary structure*, subject only to assumptions as to normal double helix geometry.[6]

To confirm the structure of the photoproduct, 5-(4-pyrimidin-2-one)cytosine (**7a**), by independent means, we devised an unequivocal synthesis of Pyo(4-5)Cyt (**7a**) which also serves as the first in a set of general methods for the synthesis of substituted bipyrimidines. In outline, it was envisaged that the ring closure of the β-methoxyacrylonitrile derivative **3** with urea might give **7a** in a single step. There are many examples of the synthesis of cytosine derivatives by this method,[9] although Russell and Hitchings have shown that in particular α-methoxymethylenephenylacetonitrile does not react with thiourea or with *S*-ethylpseudothiourea.[10]

It is known that the methyl group at C-6 of a purine[11] or C-4 of a pyrimidine[12,13] is reactive to the Vilsmeier reagent. The preparation of the key intermediate in the present synthesis, 4-(α-formylcyanomethyl)-pyrimidin-2-one (shown arbitrarily in the enol form **6**), was based upon this earlier knowledge. Reaction of 4-methylpyrimidin-2-one (**4**) with 4 molar equiv of $COCl_2$–dimethylformamide (DMF) reagent followed by treatment with hydroxylamine at pH 4.5 gave crude 4-(isoxazol-4-yl)pyrimidin-2-one (**5**). The isoxazole **5** is sufficiently unstable that it undergoes isomerization to the cyanoaldehyde **6** on drying *in vacuo* at 25°. The wet crystals of **5** could be stored for 3 days at −25° without appreciable rearrangement. To obtain pure isoxazole **5**, an alternative route through 4-(α-diformylmethyl)pyrimidin-2-one (**1**) was attempted; however, the concomitant formation of 4-(α-formylcyanomethyl)-pyrimidin-2-one (**6**) in the product could not be avoided. Treatment of the isoxazole **5** with aqueous *N* NaOH solution at 25° for 30 min gave **6** in overall yield of 53% from **4**. When alkylation of the enolic oxygen of the cyanoaldehyde **6** was attempted under a variety of conditions[14,15] using $CH_2N_2$, MeI and NaH, and triethyl orthoformate, reaction occurred primarily at N-1 of the pyrimidine. Thus, reaction of the cyanoaldehyde **6** sodium salt with MeI in DMF afforded 4-(α-formylcyanomethyl)-1-methylpyrimidin-2-one (**2**) in 76% yield. Compound **6** has five potential alkylation sites: two ring nitrogens, the oxygens of the enolic aldehyde and the ring carbonyl, and the exocyclic α-methylene. The occurrence of methylation on N-1 was proved by the nmr spectra [$(CD_3)_2SO$], which showed the methyl protons at δ 3.4, and by a nuclear Overhauser effect (NOE)[16] between the C-6 proton and the methyl protons. Thus, irradiation of the methyl signal produced a signal intensity increase (13%) in the C-6 proton (δ 8.07 ppm). The magnitude of the

(1) A. Favre, M. Yaniv, and A. M. Michelson, *Biochem. Biophys. Res. Commun.*, **37**, 266 (1969).

(2) M. Yaniv, A. Favre, and B. G. Barrell, *Nature (London)*, **223**, 1331 (1969).

(3) L. Chaffin, D. R. Omilianowski, and R. M. Bock, *Science*, **172**, 854 (1971).

(4) N. J. Leonard, D. E. Bergstrom, and G. L. Tolman, *Biochem. Biophys. Res. Commun.*, **44**, 1524 (1971). NOTE ADDED IN PROOF.—This structure has been confirmed by A. Favre, B. Roques, and J.-L. Fourrey, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **24**, 209 (1972).

(5) The symbolism employed for the bipyrimidines follows the system suggested for bipyrimidine photoproducts after discussions with Dr. Waldo E. Cohn, Director of the NAS–NRC Office of Biochemical Nomenclature [*cf.* D. E. Bergstrom and N. J. Leonard, *J. Amer. Chem. Soc.*, **94**, 6178 (1972)].

(6) D. E. Bergstrom and N. J. Leonard, *Biochemistry*, **11**, 1 (1972).

(7) D. F. Rhoades and S. Y. Wang, *J. Amer. Chem. Soc.*, **93**, 3779 (1971).

(8) D. F. Rhoades and S. Y. Wang, *Biochemistry*, **10**, 4603 (1971).

(9) D. J. Brown, "The Pyrimidines," Wiley-Interscience, New York, N. Y., 1962, p 59.

(10) P. B. Russell and G. H. Hitchings, *J. Amer. Chem. Soc.*, **73**, 3763 (1951).

(11) D. M. Brown and A. Giner-Sorolla, *J. Chem. Soc. C*, 128 (1971).

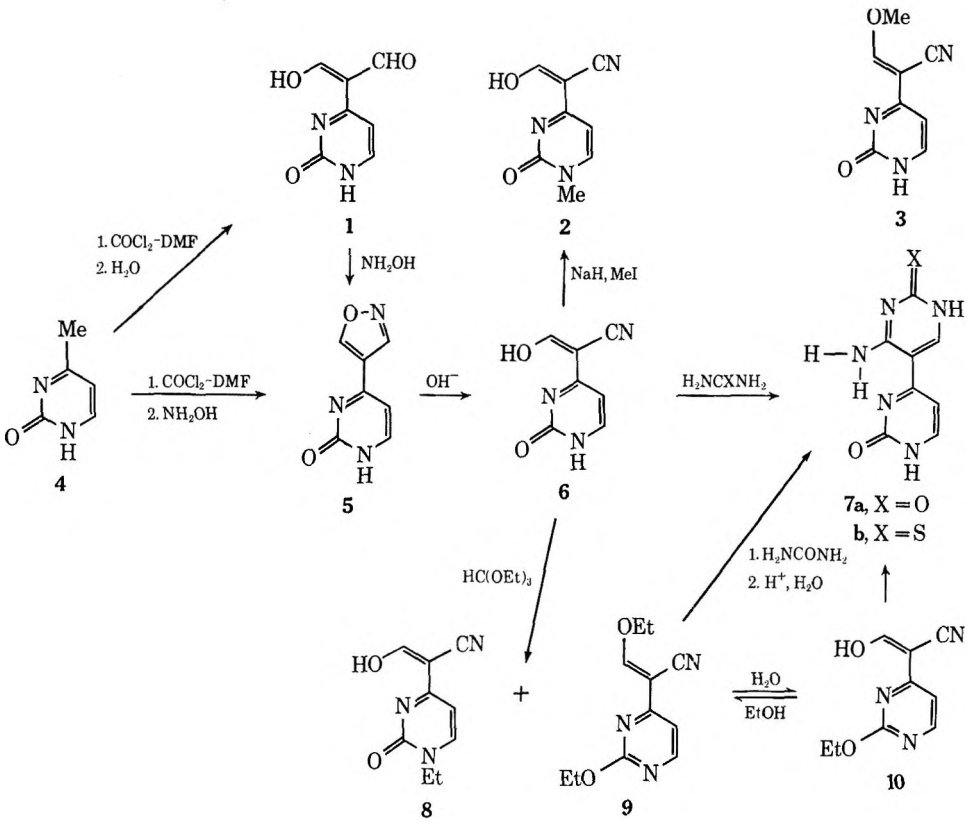
(12) H. Bredereck and G. Simchen, *Angew. Chem.*, **75**, 1102 (1963).

(13) H. Bredereck, G. Simchen, and P. Speh, *Justus Liebigs Ann. Chem.*, **737**, 46 (1970).

(14) P. B. Russell and N. Whittaker, *J. Amer. Chem. Soc.*, **74**, 1310 (1952).

(15) B. H. Chase and J. Walker, *J. Chem. Soc.*, 3518 (1953).

(16) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).



enhancement lies in the range observed for the pyrimidine nucleosides.[17,18]

Treatment of the cyanoaldehyde **6** with triethyl orthoformate under reflux gave two products: A, mp 95–97°, and B, mp 175–177°. The lower melting product showed two sets of *O*-ethyl protons in the nmr spectrum [$(CD_3)_2SO$]. The two methyl triplets were observed at $\delta$ 1.33 and 1.35 ($J$ = 7 Hz) and the two methylene quartets at 4.33 and 4.43 ($J$ = 7 Hz). The C-5 proton appeared as a doublet at $\delta$ 7.03 ppm ($J$ = 5 Hz), which is at ~0.9 ppm lower field[19] than was observed in **6** (6.02) and **2** (6.11). The uv spectrum ($\lambda_{max}^{EtOH}$ 305 nm) suggested the change from possible intramolecularly hydrogen-bonded periplanar forms **2** and **6** to preferred noncoplanar conformers in **9**. Therefore, the lower melting product was assigned the structure of 2-ethoxy-4-($\alpha$-ethoxymethylenecyanomethyl)-pyrimidine (**9**). The nmr spectrum [$(CD_3)_2SO$] of the higher melting product showed methyl and methylene proton resonances at $\delta$ 1.25 (t, 3, $J$ = 7 Hz) and 3.86 (q, 2, $J$ = 7 Hz), respectively, values which are indicative of an *N*-ethyl group. The C-5 proton signal at $\delta$ 6.10 (d, 1, $J$ = 7 Hz) falls in the comparable region with that of **2**. The NOE (7% increase of the C-6 proton) between the methylene protons and the C-6 proton was again observed. From these data the higher melting point compound was assigned structure **8**, 1-ethyl-4-($\alpha$-formylcyanomethyl)pyrimidin-2-one.

The substituted pyrimidine derivative **9** was hydrolyzed readily in neutral 30% aqueous ethanol at 25° to afford 2-ethoxy-4-($\alpha$-formylcyanomethyl)pyrimidine (**10**), which reverted to **9** merely by refluxing in absolute ethanol. The structure of **10** was supported by the C-5 proton resonance at $\delta$ 6.82 (d, 1, $J$ = 7 Hz) in the nmr spectrum, by the fact that the anilide derived from **10** was not identifiable with either of the anilides from **6** or **8**, and by the fact that the fusion reaction of **10** with urea gave Pyo(4-5)Cyt (**7a**) only after acid treatment. Moreover, the ready exchange of ethanol favors reaction at the exocyclic function rather than at the 2 position.

Since attempts at selective enolic O-alkylation were not successful, direct reactions of the cyanoaldehyde **6** with urea and with thiourea were tried. However, the reaction under the usual[9] or modified conditions—*n*-BuONa in *n*-BuOH, HCl in EtOH, HBr in AcOH, and fuming $H_2SO_4$—did not proceed in the desired direction. Nevertheless, the fusion reaction of the lithium salt of the cyanoaldehyde **6** with urea at 150° was partially successful in that the desired product 5-(4-pyrimidin-2-one)cytosine (**7a**), was obtained, albeit in very low yield. Identification of the product with Pyo(4-5)Cyt obtained from the photoreaction of 4-thiouracil with cytosine[6] was established by the criteria of the mass and uv spectra. The analogous reaction of **9** with urea was carried out, followed by acid hydrolysis, but the yield was only slightly improved. The cyclization with *S*-ethylpseudothiourea, which was also attempted, showed (by tlc) multiple product formation. Finally, the fusion reaction of the lithium salt of **6** with thiourea was investigated. However, the yield (6%) of 5-(4-pyrimidin-2-one)-2-thiocytosine, Pyo(4-5)s$^2$Cyt (**7b**), could not be improved to the extent that would be advantageous for an alternative route to **7a**. The elemental composition of **7b** was established by peak matching in the double-focusing mass spectrometer (calcd for $C_8H_7N_5OS$, 221.0371; found, 221.0372). The mass spectral fragmentation patterns, 221 ($M^+$), 163, 162, 161, 146, 135, 119, 108, 92, and 59 (base peak), were in accord with those observed for Pyo(4-5)Cyt

(17) P. A. Hart and J. P. Davis, *Biochem. Biophys. Res. Commun.*, **34**, 733 (1969).

(18) P. A. Hart and J. P. Davis, *J. Amer. Chem. Soc.*, **93**, 753 (1971).

(19) S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson, and R. A. Hoffman, *Ark. Kemi*, **22**, 65 (1964).

(**7a**). The borohydride-reduced Pyo(4-5)s$^2$Cyt (**7b**) appeared fluorescent on cellulose tlc plates, as in the case of **7a**.

The low-yield synthesis of 5-(4-pyrimidin-2-one)-cytosine (**7a**) described here accomplishes the initial and primary goal of providing an independent and direct proof of the structure of the bipyrimidine moiety formed in *E. coli* tRNAs by the photolinking of 4-thiouridine (base no. 8) and cytidine (base no. 13) under long-wavelength uv irradiation.

## Experimental Section[20]

**4-(Isoxazol-4-yl)pyrimidin-2-one (5).**—To a solution of DMF (10.2 g, 0.14 mol) in $CHCl_3$ (10 ml) was added dropwise a solution of $COCl_2$ (11.9 g, 0.12 mol) in $CHCl_3$ (22 g) at 0–5° under vigorous stirring. The mixture was stirred at 25° for 15 min and at 35° for 30 min. A neutralized solution of **4** HCl (4.4 g, 0.03 mol) with triethylamine (3.0 g, 0.03 mol) in $CHCl_3$ (20 ml) was added to the stirred reaction mixture at 25°, and the mixture was stirred at 25° for 4 hr and finally warmed at 50° for 8 hr. After cooling, the precipitate (Vilsmeier adduct) was collected by filtration and dissolved in ice–water (70 ml). To this solution was added $NH_2OH \cdot HCl$ (10.4 g, 0.15 mol) and $NaHCO_3$ (8.5 g). The mixture (pH 4.5) was kept in a refrigerator overnight and the brown crystals which formed were collected by filtration to give (wet) isoxazole **5** (8.4 g): uv (qualitative) max (pH 5.5) 315, 254 nm; uv max (pH 1.5) 329, 256; $R_f$ in system A, 0.58.

**4-(α-Formylcyanomethyl)pyrimidin-2-one (6).**—The crude isoxazole **5** (6.35 g) obtained in the reaction described above was dissolved in 1 *N* NaOH (50 ml) and kept at 25° for 30 min. The solution was decolorized with charcoal (1.0 g) and adjusted to pH 3.5 with dilute HCl. The precipitate was collected by filtration to give crude cyanoaldehyde **6** (3.0 g). Recrystallization from MeOH (570 ml) with charcoal (2.0 g) afforded a first crop (1.90 g) of pale yellow leaflets, mp 245–250° dec, and a second crop (0.10 g), from the mother liquor concentrated to a volume of 50 ml: total yield 2.0 g (54%); nmr δ 6.02 (d, 1, $J$ = 7 Hz, $C_5$ proton), 7.72 (d, 1, $J$ = 7 Hz, $C_6$ proton), 9.22 (s, 1, OCH=), 12.22 (br, 2, OH, NH); ir (KBr) 2220 cm$^{-1}$ (C≡N); uv max (EtOH) 357 nm (ε 24,410), 245 (5810), 222 (7940); uv (pH 6.9) 342 nm (ε 20,960), 283 (3200), 245 (6940); uv (pH 1.2) 353 nm (ε 24,960), 240 (4520), 223 (6780); uv (pH 12.8) 327 nm (ε 21,770), 280 (6430).

*Anal.* Calcd for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.65; H, 3.04; N, 25.77.

**4-(α-Diformylmethyl)pyrimidin-2-one (1).**—The Vilsmeier adduct of 4-methylpyrimidin-2-one which was prepared in the same manner and scale as described in the first section above was dissolved in water (70 ml) and refluxed for 15 min. After the solution cooled, fine colorless needles were collected by filtration and washed with cold water to give the crude product (2.58 g). Recrystallization from 50% aqueous EtOH with charcoal gave analytically pure **1** (2.0 g, 40%): mp 253–255° dec; nmr δ 7.39 (d, 1, $J$ = 7 Hz, $C_5$ proton), 7.85 (d, 1, $J$ = 7 Hz, $C_6$ proton), 9.55 (s, 2); ir (KBr) 1723 cm$^{-1}$ (C=O); uv max (EtOH) 361 nm (ε 25,510), 243 (12,450); uv (pH 6.9) 354 nm (ε 25,370), 262 (12,270), 228 (8830); uv (pH 1.2) 360 nm (ε 25,620), 247 (13,970); uv (pH 12.8) 353 nm (ε 8730), 313 (7960), 268 (19,960).

*Anal.* Calcd for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.36; H, 3.61; N, 16.88.

**4-(α-Formylcyanomethyl)-1-methylpyrimidin-2-one (2).**—To a solution of cyanoaldehyde **6** (163 mg, 1 mmol) in DMF (30 ml) was added NaH (60% oil dispersion, 44 mg, 1.1 mmol) in portions at 5–10° and the mixture was stirred at 25° for 30 min. Methyl iodide (169 mg, 1.2 mmol) was added to the mixture, which was stirred at 55–60° overnight. As the tlc of the reaction mixture showed the presence of the unchanged **6**, a further portion of methyl iodide (84 mg, 0.6 mmol) was added to the mixture, which was then stirred at 55–60° for another 4 hr (completion of the reaction was confirmed by tlc). The reaction mixture was concentrated to dryness *in vacuo*, washed with ether (30 ml), and recrystallized from MeOH (12 ml) to give **2** (120 mg) as colorless needles, mp 203–206°. A second crop (33 mg) was obtained from the mother liquor, mp 199–203°, and recrystallized from MeOH (3.5 ml) to give a pure product (15 mg), mp 204–207°.

The total yield was 135 mg (76%) and an analytically pure sample had mp 204–207°; nmr δ 3.40 (s, 3, $NCH_3$), 6.22 (d, 1, $J$ = 7.5 Hz, $C_5$ proton), 8.07 (d, 1, $J$ = 7.5 Hz, $C_6$ proton), 9.32 (s, 1, OCH=); ir (Nujol) 2220 (C≡N), 1720 (C=O) cm$^{-1}$; uv max (EtOH) 349 nm (ε 25,160), 249 (9000); uv (pH 6.9) 338 nm (ε 25,440), 288 (4570), 247 (6680); uv (pH 1.2) 359 nm (ε 27,850), 247 (5100), 226 (7240); uv (pH 12.8) 338 nm (ε 29,170), 287 (5970), 245 (7290).

*Anal.* Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.30; H, 3.96; N, 23.82.

**Reaction of Cyanoaldehyde 6 with Triethyl Orthoformate.**—A mixture of **6** (815 mg, 5 mmol) and triethyl orthoformate (30 ml) was refluxed gently (internal temperature, 150 ± 5°) for 33 hr. The mixture was concentrated *in vacuo*, and the residual oil was dissolved in xylene (50 ml). A small amount of insoluble precipitate was removed by filtration, and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in EtOH (35 ml), decolorized with charcoal (1.5 g), and kept at −25° overnight to afford yellow crystals (149 mg), mp 168–172°. Additional recrystallization from EtOH gave **1-ethyl-4-(α-formylcyanomethyl)-pyrimidin-2-one (8,** 103 mg) as yellow needles: mp 175–177°; nmr δ 1.25 (t, 3, $J$ = 7 Hz, $CH_2CH_3$), 3.83 (q, 2, $J$ = 7 Hz, $CH_2CH_3$), 6.10 (d, 1, $J$ = 7 Hz, $C_5$ proton), 8.00 (d, 1, $J$ = 7 Hz, $C_6$ proton), 9.20 (s, 1, OCH=), 12.57 (br, 1, OH); ir (KBr) 2220 (C≡N), 1735 (C=O) cm$^{-1}$; uv max (EtOH) 358 nm (ε 24,820), 250 (5680); uv (pH 6.9), 340 nm (ε 24,340), 288 (4170), 246 (6380); uv (pH 1.2) 359 nm (ε 27,650), 247 (4940), 225 (7120); uv (pH 12.8) 338 nm (ε 29,020), 288 (5860), 245 (7310).

*Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.43; H, 4.72; N, 21.77.

The ethanolic filtrates were combined and concentrated to dryness *in vacuo*. The residual oil was chromatographed on a silical gel column (0.2–0.05 mm, 25 g, 2.0 × 18.0 cm), elution with $CHCl_3$. The first fraction of $CHCl_3$ (110 ml) was evaporated to afford crystals (250 mg), mp 87–94°. Recrystallization from isopropyl ether gave **2-ethoxy-4-(α-ethoxymethylenecyanomethyl)pyrimidine (9)** (188 mg, 17%), mp 94–95.5°. Further recrystallization from isopropyl ether afforded an analytically pure sample: mp 95–97°; nmr δ 1.33 and 1.35 (two triplets, 6, $J$ = 7 Hz, $2OCH_2CH_3$), 4.33 and 4.43 (two quartets, 4, $J$ = 7 Hz, $2OCH_2CH_3$), 7.03 (d, 1, $J$ = 5 Hz, $C_5$ proton), 8.44 (d, 1, $J$ = 5 Hz, $C_6$ proton), 8.54 (s, 1, OCH=); ir (KBr) 2220 (C≡N), no carbonyl absorption; uv max (EtOH) 305 nm (ε 16,530), 263 (7070).

*Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.23; H, 5.86; N, 19.18.

The second fraction (45 ml) contained an unidentified compound (15 mg), mp 178–181° dec. The third fraction (125 ml) was evaporated and the residue was recrystallized from EtOH (5 ml) to give another crop of **8** (27 mg), mp 172–175°, total yield 130 mg (14%).

**2-Ethoxy-4-(α-formylcyanomethyl)pyrimidine (10).**—To a solution of **9** (438 mg, 2 mmol) in EtOH (15 ml) was added water (5 ml) and the mixture was stirred at 25° for 4 hr. The uv spectrum and tlc of the mixture after 2 hr showed completion of the hydrolysis. The mixture was concentrated to dryness *in vacuo* and the residue was triturated with isopropyl ether to give **10** (362 mg, 95%) as yellow needles: mp 205–208° dec; nmr δ 1.33 (t, 3, $J$ = 7 Hz, $OCH_2CH_3$), 4.43 (q, 2, $J$ = 7 Hz, $OCH_2CH_3$), 6.82 (br d, 1, $J$ = 7 Hz, $C_5$ proton), 7.71 (d, 1, $J$ = 7 Hz, $C_6$ proton), 9.55 (s, 2, OCH= and HO); ir (KBr) 2200 (C≡N); uv max (EtOH) 347.5 nm (ε 20,860), 273 (4220), 230 (9370); uv (pH 6.9) 326 nm (ε 23,750), 267 (5530), 227 (11,620); uv (pH 1.3) 346 nm (ε 24,930), 270 (3940), 232 (8340); uv (pH 12.7) 326 nm (ε 24,120), 266 (5440), 227 (11,530).

*Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.32; H, 4.68; N, 21.96.

(20) Melting points are uncorrected. Nmr spectra were obtained on a Varian Associates A-60 or HA-100 spectrometer using tetramethylsilane as an internal reference and $(CD_3)_2SO$ as the solvent. We thank Mr. Steve Silber for his assistance with the nmr spectra. Ir spectra were obtained on a Perkin-Elmer Model 337 grating spectrophotometer. Thin layer chromatography (tlc) was carried out on 200 × 40 × 0.16 mm Eastman chromagram sheets, cellulose without fluorescent indicator, in the following solvent systems: A, 1-propanol–water (7:3 v/v); B, ethanol–ammonium acetate (1.0 *M*) (7:3 v/v), buffered to pH 7.95 with concentrated $NH_4OH$; C, 1-butanol–water–acetic acid (80:30:12 v/v). Spots were visualized by long and short wavelength uv light. Microanalyses were performed by Mr. Josef Nemeth and his associates at the University of Illinois and by Midwest Microlab, Inc., Indianapolis, Ind.

Reconversion of **10** to **9** upon refluxing in EtOH was confirmed by uv spectroscopy. A solution of **10** (2 mg) in absolute EtOH (100 ml) was heated at reflux for 63 hr. The uv max (350 nm) of the original solution changed to the uv max (307 nm) of **9**.

**4-(α-Anilinomethylenecyanomethyl)pyrimidin-2-one.**—A mixture of **6** (163 mg, 1 mmol), aniline (102 mg, 1.1 mol), and DMSO (1 ml) was heated at 110 ± 5° for 1.5 hr. After cooling, the mixture was triturated with isopropyl ether and EtOH. The crystals were collected by filtration and washed with a small amount of EtOH to give the anilide (197 mg). Recrystallization twice from DMF–EtOH (1:1, 20 ml) gave analytically pure sample (90 mg, 38%) as greenish needles, mp 262–265° dec.

*Anal.* Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.71; H, 4.29; N, 23.31.

**4-(α-Anilinomethylenecyanomethyl)-1-ethylpyrimidin-2-one.**—A mixture of **8** (191 mg, 1 mmol), aniline (102 mg, 1.1 mmol), and DMSO (2 ml) was heated at 100–110° for 7 hr and worked up in the manner described above to give crude anilide (211 mg). Recrystallization from EtOH (5 ml) gave the anilide (147 mg, 55%) as yellow needles: mp 197–198°; nmr δ 1.25 (t, 3, $J$ = 7 Hz, $NCH_2CH_3$), 3.83 (q, 2, $J$ = Hz, $NCH_2CH_3$), 6.32 (d, 1, $J$ = 7 Hz, C-5 proton), 7.0–7.5 (m, 6, phenyl protons and NH), 8.01 (d, 1, $J$ = 7 Hz, C-6 proton).

*Anal.* Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.54; H, 5.38; N, 20.76.

**4-(α-Anilinomethylenecyanomethyl)-2-ethoxypyrimidine.**—A mixture of **10** (89 mg, 0.47 mmol), aniline (48 mg, 0.51 mmol), and DMSO (1 ml) was heated at 110 ± 5° for 2 hr and worked up in the manner described above to give the anilide (105 mg). Recrystallization from EtOH (10 ml) gave yellow plates (82 mg, 66%), mp 165–166°, which were recrystallized again from EtOH for analysis.

*Anal.* Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.75; H, 5.42; N, 20.88.

**Fusion Reaction of Cyanoaldehyde 6 Lithium Salt with Urea.**—To a suspension of **6** (163 mg, 1 mmol) in water (4 ml) was added 1 *N* LiOH (1 ml) at 25°. The solution was concentrated to dryness *in vacuo* and the residual crystals were dried at 65° overnight. A finely powdered mixture of cyanoaldehyde **6** lithium salt (1 mmol) and urea (5 g) was heated at 148 ± 2° (bath temperature) for 2 hr. After cooling, the mixture was dissolved in water (10 ml), filtered, and washed with water (10 ml). The combined filtrate and washings were neutralized with 1 *N* HCl, and the precipitate was removed by filtration. The filtrate was chromatographed on an IRC-50 ion-exchange resin column (2.5 × 7.5 cm), elution with water. The first 1.8 l. of eluent was discarded and the next 4.8 l. was concentrated to a volume of 80 ml. The precipitate was collected by filtration and dried at 65° *in vacuo* for 2 hr to give Pyo(4-5)Cyt (**7a**, 5.6 mg, 2.5%), mp >310°. The sample was dried at 78° for 30 hr *in vacuo* for elemental analysis. The uv and mass spectra and the tlc behavior were identical with those of the Pyo(4-5)Cyt that had been obtained in the photoreaction of cytosine and 4-thiouracil.

*Anal.* Calcd for $C_8H_7N_5O_2 \cdot H_2O$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.47; H, 4.30; N, 31.30.

**Fusion Reaction of 9 with Urea.**—A mixture of **9** (110 mg, 0.5 mmol) and urea (1.0 g) was heated at 145 ± 3° for 1 hr. The mixture was dissolved in 0.05 *N* HCl (10 ml) and heated at 80–85° for 6 hr. The brown precipitate was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residue was extracted with concentrated $NH_4OH$ (4 ml), and the extract was chromatographed on a G-15 Sephadex column (72 × 2.2 cm), elution with a pH 10 $(NH_4)_2CO_3$–$NH_4OH$ buffer (0.1 *M*). Fractions of Pyo(4-5)Cyt, which can be detected by tlc,[5] were collected and evaporated to dryness. The residual crystals were washed with water (5 ml) and MeOH (1 ml) to give crude **7a** (8.4 mg, 4.6%). The purity of the **7a** (56.5%) was determined by quantitative uv analysis. Compound **7a** could also be isolated (4.8%) from the fusion of **10** with urea under similar conditions.

**The Fusion Reaction of Cyanoaldehyde 6 Lithium Salt with Thiourea.**—A mixture of **6** lithium salt (prepared in the same manner described above, 17 mg, 0.1 mmol) and thiourea (500 mg) was heated at 180 ± 2° (bath temperature) for 1 hr. After cooling, the mixture was dissolved in water (5 ml) and the precipitate was collected by filtration. The precipitate was extracted with 1 *N* HCl (5 ml). The filtrate was passed through an IRC-50 ion-exchange resin column ($H^+$ form, 1.5 × 10 cm). After being washed with water (50 ml), the column was eluted with 1 *N* HCl (200 ml). The eluate was evaporated to dryness *in vacuo*. The residue was combined with the 1 *N* HCl extract (5 ml) of the precipitate and this 1 *N* HCl-soluble portion was concentrated to dryness *in vacuo*. The residue was dissolved in concentrated $NH_4OH$ (2.5 ml) and chromatographed on a G-15 Sephadex column (72 × 2.2 cm), elution with a pH 10 $(NH_4)_2CO_3$–$NH_4OH$ buffer (0.1 *M*). Fractions of 8.6 ml were collected. Fractions 76–101 were combined and evaporated to dryness *in vacuo*. The residue was dissolved in concentrated $NH_4OH$ (2.5 ml) and filtered. The filtrate was concentrated to dryness and residual crystals were collected and washed with water (2 ml) and with MeOH (0.5 ml) to give **5-(4-pyrimidin-2-one)-2-thiocytosine** (**7b**, 1.3 mg, 5.8%) as a yellow powder: mp >310°; $R_f$ 0.17 in system A, 0.19 in B, 0.14 in C; a bright blue fluorescent spot (long-wave uv) after spraying with an ethanolic sodium borohydride solution; mass spectrum (70 eV) *m/e* (>10% rel intensity) 222 (13), 221 (91), 220 (14), 204 (14), 203 (13), 188 (16), 179 (14), 166 (12), 163 (52), 162 (23), 161 (27), 146 (29), 145 (16), 136 (20), 135 (28), 120 (20), 119 (26), 118 (18), 108 (20), 107 (17), 93 (18), 92 (20), 91 (16), 87 (19), 80 (11), 76 (10), 74 (31), 68 (12), 67 (18), 66 (20), 65 (18), 64 (19), 60 (11), 59 (100), 58 (12), 55 (11), 53 (14), 52 (28), 44 (38), 43 (53), 42 (16), 41 (27), 40 (25), 39 (14), 38 (13), 36 (19), 34 (83), 33 (35), 32 (85), 29 (12), 28 (71), 27 (24); elemental composition by high resolution mass spectrometry calcd for $C_8H_7N_5OS$, 221.0371; found, 221.0372.

**Nuclear Overhauser Effects in 2 and 8.**—Spectra (Table I) were recorded using an HA-100 spectrometer in the frequency sweep mode using nitrogen-sparged $(CD_3)_2SO$ solutions with tetramethylsilane as an internal field frequency lock. The irradiation audio oscillator was a Wavetek voltage controlled generator, Model 111, with an impedance matching transformer. Power requirements were ascertained by increasing the output slowly in 10 mV increments until a signal increase was noted. Each peak of interest was integrated at least six times.

TABLE I

NUCLEAR OVERHAUSER EFFECTS IN 2 AND 8

| Compd | Group irrd[a] (δ, ppm) | H obsd (δ) | Intensity increase, % |
|---|---|---|---|
| 2 | $NCH_3$ (3.40) | $C_6$ proton (8.07) | 13 |
| 8 | $NCH_2CH_3$ (3.86) | $C_6$ proton (8.09) | 7 |

[a] Irradiated by 40 mV.

**Registry No.**—**1**, 36508-33-5; **2**, 36508-32-4; **5**, 36508-34-6; **6**, 36508-35-7; **7a**, 33604-46-5; **7b**, 36508-37-9; **8**, 36508-38-0; **9**, 36508-39-1; **10**, 36508-40-4; cytosine, 14987-28-1; 4-thiouracil, 591-28-6; 4-(α-anilinomethylenecyanomethyl)pyrimidin-2-one, 36508-41-5; 4-(α-anilinomethylenecyanomethyl)-1-ethylpyrimidin-2-one, 36508-42-6; 4-(α-anilinomethylenecyanomethyl)-2-ethoxypyrimidine, 36508-43-7.

**Acknowledgment.**—This work was supported by Research Grant GP-8407X from the National Science Foundation.

# Synthesis and Acid-Catalyzed Rearrangement of Iso-*p*-anisylapocamphene[1]

DAVID L. ADAMS[2] AND WYMAN R. VAUGHAN*

*Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06268*

*Received January 20, 1972*

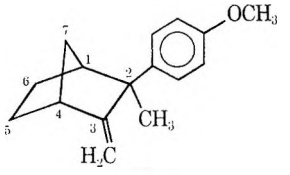
A stereospecific synthesis of iso-*p*-anisylapocamphene (**1**) and its methyl-deuterated analog (1-$CH_3$-*d*) are described. In concentrated sulfuric acid solution **1** generates the long-lived *p*-anisylcamphenilyl cation **5**, which undergoes rapid racemization. It is suggested that racemization involves a 6,2-hydride migration preceded and followed by Wagner–Meerwein rearrangements. Racemization of the cation **5** *via* cyclene formation, in contrast to the results found for the same ion in 98+% formic acid, does not take place in concentrated sulfuric acid. The differences in the nature and velocity of the racemization processes of cation **5** in 98+% formic acid and concentrated sulfuric acid are discussed in terms of the different $H_0$ values of the two solvents.

One of the more germane questions which remains unresolved in the area of cationic transformations in the norbornyl series is that of the observed exo stereospecificity of 3,2 shifts.[3] It is likely that the same phenomena responsible for predominant exo attack on 2-norbornyl cations during solvolysis are also responsible for the exclusive exo nature of 3,2 shifts in the same cations.[4] A complete understanding of the factors responsible for stereospecific 3,2 shifts is necessary if one hopes to comprehend the larger question of the nature of substituted 2-norbornyl cations.

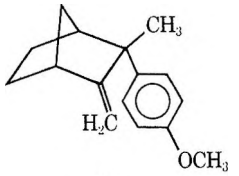
Several rationalizations have evolved in attempts to explain 3,2 shifts in these cations.[4,5] These rationalizations are extensions of more comprehensive theories dealing with the behavior of 2-norbornyl esters during solvolysis. Schleyer has offered convincing arguments against both the steric and nonclassical theories as providing adequate explanations for the observed 3,2 shifts[4] and, as an alternative, has advanced the torsional strain theory. However, recent data suggest that the influence of torsional strain in reactions of the norbornyl skeleton is minimal.[6] Although much data has been collected regarding the stereochemistry and kinetics of 3,2 shifts[7] (mainly 3,2 hydrogen shifts), presently there is no single theory which adequately accounts for the observed stereospecificity of 3,2 shifts in substituted norbornyl cations while remaining consistent with other known properties of the same ions.[8] The work of Wilder and coworkers[9,10] has produced the first examples of endo 3,2 shifts which constitute a major reaction pathway. The bornyl system is implicated in their work and is in sharp contrast to the analogous norbornyl system, which scrupulously avoids the endo 3,2 shift.[11] Certainly further research on this interesting dichotomy is suggested.

It was felt that the above dilemma was due in part to the lack of experiments designed to probe directly for fundamental phenomena responsible for the stereospecific 3,2 shifts in the norbornyl system. Therefore, this research was initiated in an attempt to begin this probe and at the same time extend the present scope of knowledge of 3,2 carbon shifts in the norbornyl system. As part of this objective it was proposed to prepare precursors which might tend to promote previously unobserved 3,2 shifts in substituted norbornyl cations. Analysis of the behavior of the precursors under cationic conditions would allow conclusions to be drawn regarding the nature of the presumed shifts and possibly the nature of the intermediate ions involved.

The precursor chosen for the present study was *exo*-2-*p*-anisyl-*endo*-2-methyl-3-methylenenorbornane (**1**)




**1**




**2**

(iso-*p*-anisylapocamphene). Since Bartlett, *et al.*,[12] have studied its epimer *p*-anisylapocamphene (**2**) extensively under cationic conditions, one is indirectly aware of much of the chemistry of **1**. Although there is no literature precedent for aryl 3,2-bridging in substituted norbornyl cations,[11-14] it was felt that **4**, produced *via* protonation of **1**, should have a good opportunity for bridging between C-2 and C-3 because (1) the *p*-anisyl group is in the favorable exo position and (2) the bridged ion **3** should benefit from the stabilizing ability of the *p*-methoxy group. Ion **4** also contains features which should serve to promote an endo 3,2-methyl migration. Such a migration will lead to the highly delocalized anisylic ion **5** and the activation energy for migration should be decreased due to partial formation of **5** at the transition state. This lowering of the activation energy could conceivably make endo 3,2-methyl migration competitive with other rearrangement pathways.

(1) Abstracted from the Ph.D. Dissertation of David L. Adams, The University of Connecticut, 1971.

(2) NDEA Fellow, 1967–1970; Texaco Fellow in Organic Chemistry, 1970–1971.

(3) See A. F. Fry and G. Karabatsos in "Carbonium Ions," Vol. II, G. A. Olah and P. von R. Schleyer, Ed., Interscience, New York, N. Y., 1970, Chapter 14, pp 521–571.

(4) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699, 701 (1967), and references cited therein.

(5) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

(6) S. P. Tindal and T. T. Tidwell, *Tetrahedron Lett.*, 783 (1971), and references cited therein. For a further view see J. W. Meller and C. F. Webb, *ibid.*, 4025 (1972).

(7) C. J. Collins and C. E. Harding, *Justus Liebigs Ann. Chem.*, **745**, 124 (1971), and references cited therein.

(8) See C. W. David, B. W. Everling, R. J. Killian, J. B. Stothers, and W. R. Vaughan, manuscript submitted for publication, The University of Connecticut and The University of Western Ontario, 1972, for suggestions regarding the possible geometrical control of 3,2 shifts in the norbornyl series and the first example of endo 3,2-methyl shift.

(9) A. W. Bushell and P. Wilder, *J. Amer. Chem. Soc.*, **89**, 5721 (1967).

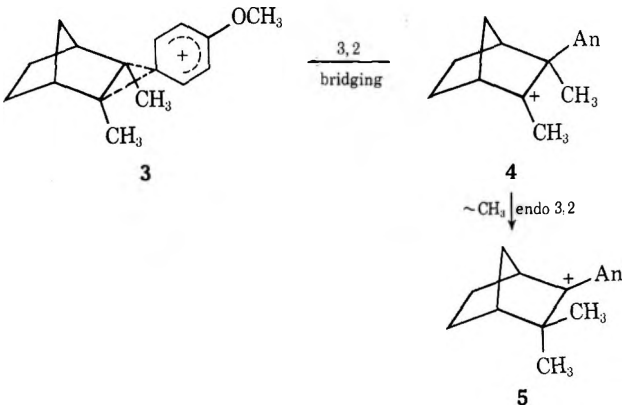
(10) P. Wilder and W.-C. Hsieh, *J. Org. Chem.*, **36**, 2552 (1971).

(11) C. J. Collins, Z. K. Chema, R. G. Werth, and B. M. Benjamin, *J. Amer. Chem. Soc.*, **86**, 4913 (1964).

(12) P. D. Bartlett, E. R. Webster, C. E. Dills, and H. G. Richey, Jr., *Justus Liebigs Ann. Chem.*, **623**, 217 (1959).

(13) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *J. Amer. Chem. Soc.*, **88**, 5350 (1966).

(14) C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *ibid.*, **89**, 3940 (1967).




## Results and Discussion

**Synthesis of Iso-*p*-anisylapocamphene (1).**—The key step in the synthesis of **1**, regardless of which route is selected, is that which controls the stereochemistry at C-2. During this step the *p*-anisyl group must assume an exo orientation. The pathway which suggests itself is the Diels–Alder reaction between cyclopentadiene and *p*-anisylmaleic anhydride (**6**). This reaction would serve both to construct the bicyclic framework and, in accord with the Alder endo rule, place the *p*-anisyl group in the exo position.

Since none of the published procedures[15] for *p*-anisylmaleic anhydride gave workable quantities, a new synthesis of **6** was developed. Ethyl anisylglyoxylate (**7**) was prepared from anisole (**8**) according to the procedure of Kindler, *et al.*[16] Keto ester **7** was converted *via* an Emmons[17] reactio nusing triethyl phosphonoacetate to the diester **9**, which was subsequently saponified to the corresponding diacid **10**. The diacid **10** was cyclized by a modification of the procedure of Vaughan, *et al.*,[18] to *p*-anisylmaleic anhydride (**6**) in 29% overall yield from **8**.

Reaction of **10** with cyclopentadiene in benzene–acetone followed by basic hydrolysis gave the unsaturated diacid **11**. Redissolution of **11** into aqueous potassium hydroxide followed by catalytic hydrogenation gave the saturated diacid **12**, and treatment of **12** with acetic anhydride overnight afforded the anhydride **13**.

Reaction of the anhydride **13** with liquid dimethylamine gave the acid salt amide **14**.[19] Attempts to convert **14** to the free acid amide by treatment with acid led to partial (60%) recyclization to the anhydride **13**, a result which is anomalous in the current literature.[19,20] However, direct reduction of the acid salt amide **14** with lithium aluminum hydride in tetrahydrofuran gave the desired amino alcohol **15**. Treatment of **15** with 30% hydrogen peroxide in methanol yielded the amine oxide alcohol **16**, which in turn yielded the unsaturated alcohol **17** upon thermal decomposition at 160°.

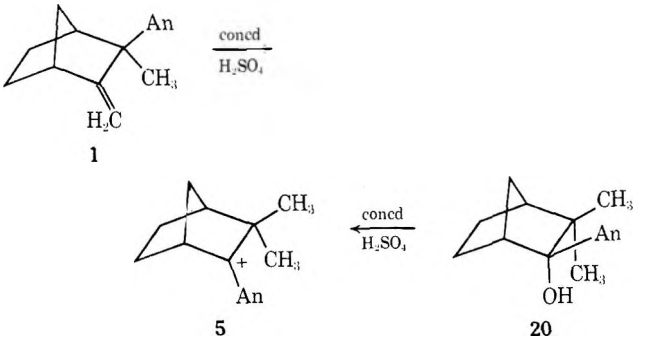
Reaction of **17** with *p*-toluenesulfonyl chloride in pyridine afforded a tosylate which reacted with lithium aluminum hydride under a variety of solvent and temperature conditions to give an unidentified product mixture which exhibits no exocyclic methylene protons in the nmr spectrum. Consequently, an alternative route for replacement of hydroxyl by hydrogen was developed.

Oxidation of alcohol **17** with chromium trioxide and pyridine in methylene chloride according to the procedure of Ratcliff and Rodehorst[21] gave the corresponding unsaturated aldehyde **18**, which was converted to its semicarbazone **19** by the usual method; and decomposition of **19** with powdered potassium hydroxide according to the procedure of Linstead and Cook[22] led to the desired iso-*p*-anisylapocamphene (**1**).

This final modified Wolff–Kishner reaction was particularly useful since it provided a method for deuterium incorporation into the methyl group. Thus, decomposition of **19** with potassium deuteroxide prepared from potassium *tert*-butoxide and deuterium oxide led to **1**-$CH_3$-*d*. Mass spectral analysis showed the **1**-$CH_3$-*d* to be a mixture of deuterated species: 22.6% $d_0$, 47.9% $d_1$, 27.5% $d_2$, and 2.0% $d_3$. The complete synthesis of **1** is illustrated in Scheme I.

The validity for assigning the exo configuration to the *p*-anisyl group in **1** rests on several grounds: (1) comparision of **1** with its known epimer **2**[12,23] *via* nmr spectra and chemical behavior; (2) the demonstrated preference of the phenyl group for the exo configuration during the related Diels–Alder reaction of phenylmaleic anhydride with cyclopentadiene;[24] and (3) the general character of the synthesis, which in principle can only lead either to **1** or **2**, and clearly does not lead to **2**.

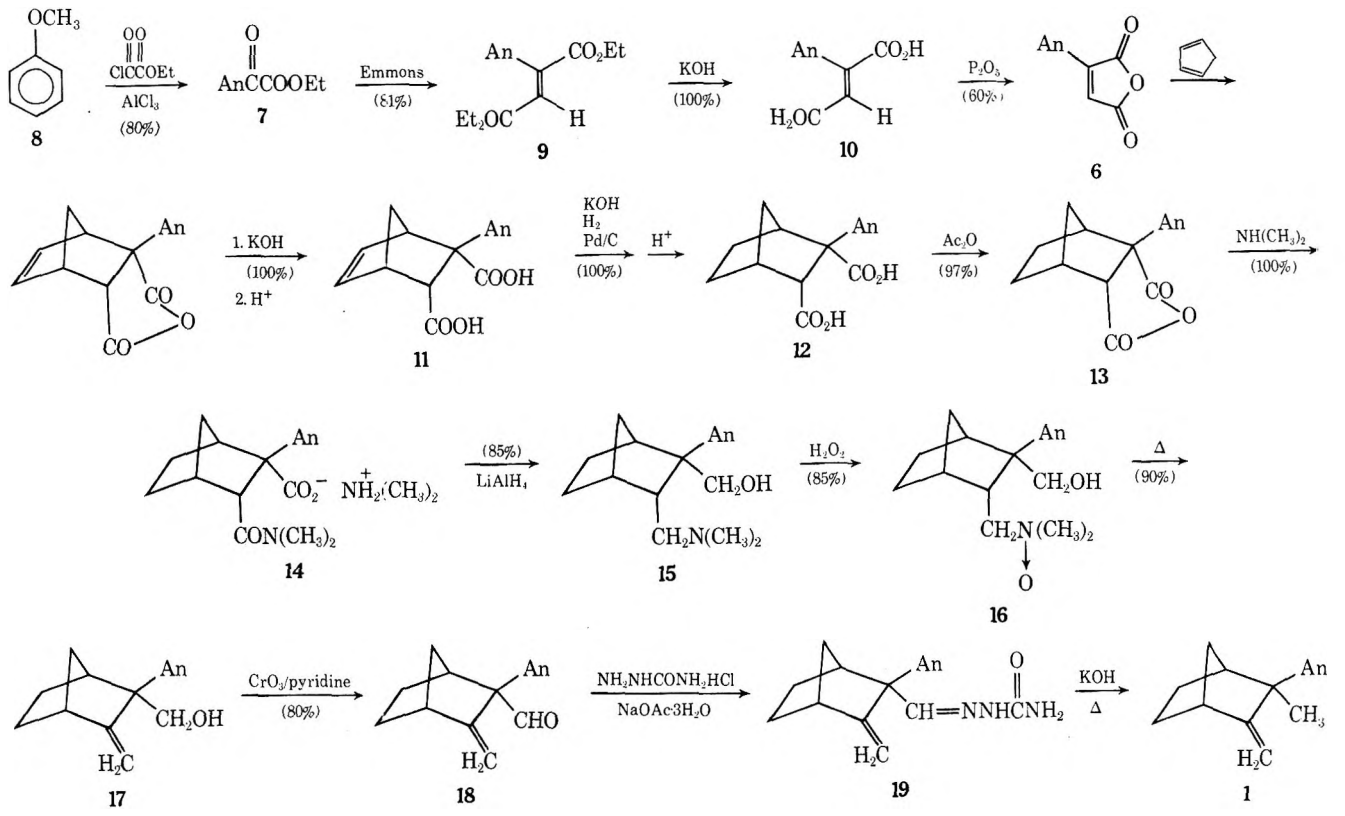
**Study of Iso-*p*-anisylapocamphene (1) in Acid Solution.**—Iso-*p*-anisylapocamphene (**1**) dissolves in concentrated sulfuric acid with formation of the orange-red, long-lived *p*-anisylcamphenilyl cation (**5**).[12] This is readily demonstrated by comparison of the visible and nmr spectra (see Experimental Section), and aqueous quenching products of a solution of **1** in concentrated sulfuric acid with those of an authentic sample of **5** generated directly from *p*-anisylcamphenilol (**20**).[12]




The possibility that the stable carbonium ion derived from **1** might be the symmetrical bridged species **3**, derived by exo 3,2 *p*-anisyl migration, is excluded by the following observation. The nmr spectrum of the carbonium ion derived from **1** in trifluoroacetic acid

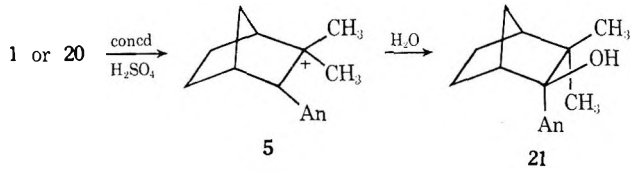
(15) See R. K. Hill, *J. Org. Chem.*, **26**, 4745 (1961).
(16) K. Kindler, W. Metzendorf, and D-y-Kwok, *Chem. Ber.*, **76**, 308 (1943).
(17) W. S. Wadsworth, Jr., and W. E. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).
(18) W. R. Vaughan and K. S. Andersen, *ibid.*, **77**, 6702 (1955).
(19) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *ibid.*, **85**, 2282 (1963).
(20) A. Foucaud, *Bull. Soc. Chim. Fr.*, 873 (1963).
(21) R. Ratcliff and R. Rodehorst, *J. Org. Chem.*, **35**, 400 (1970).
(22) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).
(23) G. B. Herschbach, Ph.D. Thesis, Harvard University, 1968, has isolated **1** in small quantities from rearrangement of **20** in formic acid. Its exo *p*-anisyl nature has been rigorously defined and Herschbach's **1** is identical with that prepared in the present study.
(24) G. I. Poos and M. M. Lehman, *J. Org. Chem.*, **26**, 2575 (1961).

SCHEME I



contains two nonequivalent methyl groups. This nonequivalence is consistent with **5** but inconsistent with formulation **3** where both methyl groups are identical.

Confirmation of **5** as the stable species in concentrated sulfuric acid is deduced from quenching experiments. Rapid addition of the carbonium ion solution to ice water produces iso-*p*-anisylcamphenilol (**21**) as the major product. Similiar quenching of a concentrated sulfuric acid solution of **20** also produces **21**.[12] If **3**, or



any slightly unsymmetrical version thereof, constituted a correct formulation for the stable carbonium ion, a structurally different alcohol would be produced upon quenching.

In an attempt to determine the pathway for the rearrangement **4** → **5**, the decision was made to generate the stable ion **5** from suitable deuterium-labeled precursors in concentrated sulfuric acid and then to trap the carbonium ion as the alcohol **21** by aqueous quenching. Subsequent nmr and mass spectral analysis of **21** would reveal the quantity and location of the original deuterium label.

From ion **4** there are potentially three distinct pathways to **5**, of which one involves exo 3,2-aryl migration. The net result of such a shift is racemization and interconversion of the two methyl groups. Since published evidence in aryl-substituted norbornyl cation systems argues against an exo 3,2-aryl shift,[11-14] it is most reasonable to consider pathways which avoid such a migration. Therefore, although exo 3,2-aryl migration cannot be ruled out by the present work, it will not be considered in the discussion.

Of the remaining two pathways the most direct route for this conversion is an endo 3,2-methyl migration, which predicts that a deuteriomethyl group originally at C-3 would be found as the endo C-2 methyl group of the isolated alcohol **21**. Similarly, a deuteriomethyl group originally at C-2 would be found as the exo C-2 methyl group.

The remaining potential route involves preliminary Wagner–Meerwein rearrangement, 6,2-hydride shift, and Wagner–Meerwein rearrangement again,[11,25] followed by exo 3,2-methyl shift. This pathway predicts that a deuteriomethyl group originally at C-3 will be found as the exo methyl group of the alcohol **21**. Similarly, a deuteriomethyl group at C-2 will be found as the endo C-2 methyl group.

Since deuterium analysis of **21** involves relative integration of the methyl signals, it is critical to establish correct assignments and record accurate integral traces for the three methyl groups. The nmr spectrum of **21** shows three sharp methyl singlets. The methoxy methyl is found at $\delta$ 3.79 and is unobscured by other absorptions. The two aliphatic methyl groups appear at $\delta$ 0.80 and 1.29, the signal at 0.80 falling at relatively high field when compared with other methyls found in the same series.[26,27] Because of the shielding by the cis *p*-anisyl group, the high-field methyl singlet is un-

(25) E. Huang, R. Ranganayakulu, and T. S. Sorensen, *J. Amer. Chem. Soc.*, **94**, 1780 (1972).

(26) The methyl signals of *endo*-3-*p*-anisyl-*exo*-2,3-dimethyl-*endo*-2-norbornanol appear at $\delta$ 1.7 and 1.38,[23] and those for *exo*-3-*p*-anisyl-2,2-dimethylnorbornane appear at $\delta$ 0.50 and 1.20.[23]

(27) The methyl signals for methylcamphenilol appear at $\delta$ 0.90 and 0.93: R. J. Kilian and W. R. Vaughan, personal communication, The University of Connecticut, 1971.

TABLE I

INTEGRATION[a] AREAS FOR ISO-*p*-ANISYLCAMPHENILOL (21) OBTAINED FROM THE VARIOUS REARRANGEMENT EXPERIMENTS

| Source | Acid | Aromatic | $C_1$ H syn 7-H | $OCH_3$ | OH | exo 3-$CH_3$ | $CH_2$'s | endo 3-$CH_3$ | Run |
|---|---|---|---|---|---|---|---|---|---|
| **20** | $H_2SO_4$ | 3.74 | 1.78 | 3.00 | | 2.99 | 6.21 | 3.05 | 1 |
| **20** | $D_2SO_4$ | 3.74 | 1.97 | 3.00 | | 2.87 | 6.04 | 2.85 | 2 |
| **2** | $D_2SO_4$ | 3.84 | 2.00 | 3.00 | 0.84 | 2.37 | 6.04 | 2.60 | 3 |
| **1** | $D_2SO_4$ | 3.69 | 2.03 | 3.00 | 1.14 | 2.54 | 6.06 | 2.52 | 4 |
| 1-$CH_3$-*d* | $H_2SO_4$ | 3.26 | 1.68 | 3.00 | | 2.02 | 6.04 | 2.14 | 5 |

[a] All integrations are the average of four determinations and are relative to the $OCH_3$ signal (3.00). Error estimated to be ±0.05 ppm based on the results of run 1.

obscured and assigned to the endo 3-methyl group;[28] but the exo 3-methyl signal falls in the absorption region of the methylene protons and cannot be accurately integrated in the normal spectrum. This problem was solved by recording spectra of the alcohol **21** after complexation with tris(dipivalomethanato)europium(III).[29] In accordance with the recent findings[30] of greater induced pseudocontact shift with decreasing distance from the coordinating center, the exo methyl group is shifted 1.89 ppm to lower field and the endo methyl group is shifted 0.88 ppm to lower field, both to unobscured portions of the spectrum.

After the analytical technique for analysis had been established, 1-$CH_3$-*d* was dissolved in concentrated sulfuric acid and quenched with water to form alcohol **21**, and **21** was purified and analyzed for deuterium content. Similar procedures were followed for **1**, **2**, and **20** in concentrated deuteriosulfuric acid. The results of these experiments are tabulated in Table I.

It is immediately obvious from runs 3, 4, and 5 that deuterium is found in both methyls in approximately equal amounts. In order to explain the labeling results in terms of only the two pathways considered above, one is forced to assume that half of the alcohol **21** is formed *via* one path and half *via* the second path. This would be a highly fortuitous result, requiring two very different pathways to have nearly identical rates, and seems very unlikely.

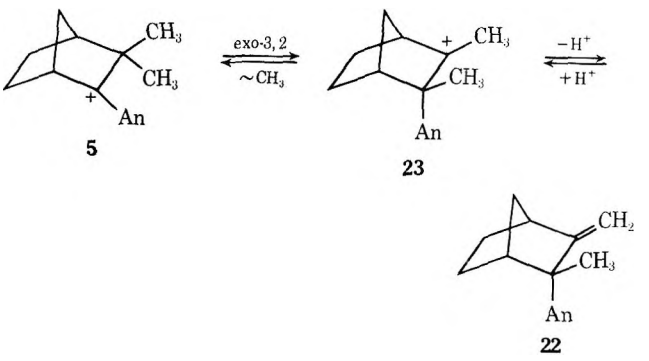
Consequently, the possibility that the *p*-anisylcamphenilyl cation (**5**) might itself be undergoing rearrangement subsequent to its formation must be considered. Run 2 (Tables I and II) shows that when cation **5** is generated directly from **20** in deuteriosulfuric acid only small amounts of deuterium enter the two methyl groups, establishing that equilibration with the neutral olefin **22** is slow. This result is in contrast to the rapid equilibrium between **5** and **22** in 98+% formic acid.

TABLE II

DEUTERIUM ANALYSES[a] OF ISO-*p*-ANISYLCAMPHENILOL (21) OBTAINED FROM THE VARIOUS REARRANGEMENT EXPERIMENTS

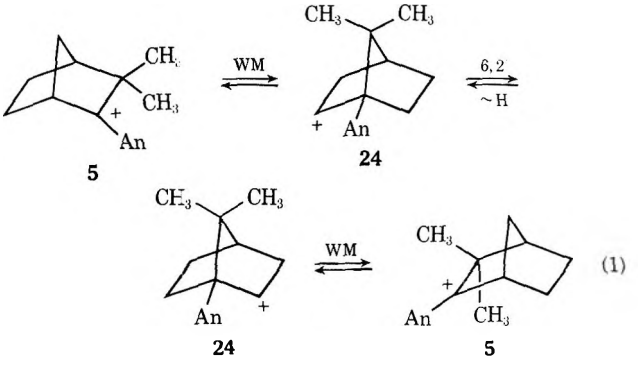
| | | Percentage | | | | |
|---|---|---|---|---|---|---|
| Source | Acid | $d_0$ | $d_1$ | $d_2$ | $d_3$ | Run |
| **20** | $D_2SO_4$ | 95.89 | 3.55 | 0.55 | | 2 |
| **1** | $D_2SO_4$ | 4.35 | 88.67 | 6.89 | 0.09 | 4 |
| 1-$CH_3$-*d* | $H_2SO_4$ | 20.76 | 48.00 | 29.24 | 1.99 | 5 |

[a] Percentages of the deuterated isomers were calculated in the usual fashion from the $(M - 18)^+$ peak.




This loss of a proton with formation of a neutral molecule is strongly inhibited in concentrated sulfuric acid, owing to its highly ionizing nature and the absence of sufficiently basic species to assist in proton removal.

Since Bartlett's[12] original work with ion **5** in 98+% formic acid showed only small amounts of racemization in the ion after 24 min, the possibility of a racemizing process such as path 1 was initially disregarded. It will be noted that the net result of path 1 is racemization of the cation and interconversion of the methyls under equilibrium conditions. In order to test for the operation of path 1 in concentrated sulfuric acid, optically active *p*-anisylcamphenilol (**20**), $[\alpha]_D$ −24.7° (*c* 6.2, benzene), was subjected to the usual rearrangement conditions in sulfuric acid, and the **21** isolated was found to be racemic within experimental error after 2 min.



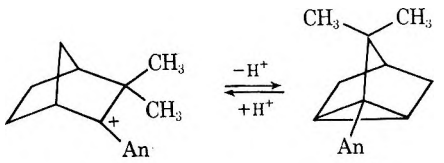

Thus, the equal deuterium distribution in the exo and endo methyl groups of **21** isolated from the rearrangement experiments is explained by the operation of a racemizing process subsequent to the formation of ion **5**. The deuterium studies are inconclusive regarding the actual rearrangement pathway for **4** → **5** since, regardless of which methyl group contains the label after the initial rearrangement, the equilibration reaction will distribute equal quantities of deuterium to both methyls.

(28) See B. L. Shapiro, M. J. Gattuso, H. P. Hepfinger, R. L. Shore, and W. C. White, *Tetrahedron Lett.*, 219, 223 (1971), for further examples of methyl shielding due to aromatic nuclei in constrained ring systems.

(29) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

(30) P. V. DeMarco, T. K. Elzey, A. F. Fentamin, and R. L. Foltz, *ibid.*, **92**, 5734, 5737 (1970).

A process having identical mechanistic consequences with path 1 involves a rapid equilibrium between the cation **5** and the symmetrical cyclene **25**, which has




**5** **25**

been isolated from 98+% formic acid solutions of **20**; and Bartlett, *et al.*, invoke it to explain the partial racemization of **2** in this acid.[31] However, the results of run 2 (Tables I and II) indicate no significant deuterium incorporation into the methylene positions of **5** when the ion is generated in concentrated deuteriosulfuric acid. Since a rapid equilibrium between **5** and **25**, necessary to account for total racemization, would involve significant multiple deuterium incorporation, **25** cannot account for the racemization observed in concentrated sulfuric acid. Accordingly, we propose that the principal mechanism resulting in racemization is path 1, although it is possible that some reacemization occurs *via* **25**, but to an extent undeterminable by the present methods.

Facile formation of the symmetrical cyclene **25** in 98+% formic acid contrasts with its apparently difficult formation in concentrated sulfuric acid. This is explained by an argument similar to that cited to account for the increased formation of olefin **22** from **5** in formic acid relative to concentrated sulfuric acid. In 96.8% formic acid ($H_0 = -0.90$)[31] the concentration of the stable carbonium ion **5** decreases to 58% of its initial concentration after 2 min, and to 18% of its initial concentration after 10 min. The decrease in concentration of **5** is due to the rapid reversible formation of olefin **22**. From a solution of optically active **20** in 98+% formic acid after 9 min the olefin **22**, still containing a substantial portion of the optical activity, can be isolated in 67% yield.[12] This demonstrates that equilibration of **5** with **22** is much faster than conversion of **5** to the cyclene **25**. Some racemization due to the formation of **25** does occur, however, and its observed rate is governed by the concentration of **5**; since this decreases rapidly in formic acid, only minor amounts of racemization take place in this acid.

Under the experimental conditions for these racemization studies in formic acid,[12] alcohol **20** was dissolved completely as the ion **5**, but the olefin **22** separated as it was formed. When a formic acid–petroleum ether (bp 30–60°) mixture was used, shaking was continued throughout the experiment, thereby preserving active equilibrium between the phases and causing the olefin to restore the concentration of **5**, which then yields the cyclene **25**, isolated in 32% yield after a few minutes. Bartlett has accordingly attributed the increased cyclene formation (*i.e.*, racemization) to the higher ion concentration.[31]

In concentrated sulfuric acid ($H_0 = -10.27$)[32] ion **5** is fully formed and its concentration does not decrease for long periods of time, as evidenced by the persistence of the visible absorption due to the ion. This is attributable to the previously discussed inhibited formation of both **22** and **25** in this solvent. The small amount of **22** which forms is rapidly converted to its conjugate acid **23** in the highly acidic medium. Therefore, **5** enjoys a continuously high concentration in concentrated sulfuric acid, and the observed rates of the transformations of path 1 are increased to the point where racemization (*i.e.*, epimerization) is a rapid process, much faster than equilibration with the olefin **22**.

It is difficult to understand the rearrangement of the stable anisylic ion **5** to the secondary ion **24** in terms of classical intermediates. For this reason, in a related sequence during the pinacol rearrangement of *endo*-2-phenylnorbornane-*cis*,*exo*-2,3-diol, Collins chose to represent the ions as nonclassical.[11] In view of the growing body of evidence that 2-aryl-2-norbornyl cations are classical,[33] ion **5** is best represented as an open anisylic cation. However, the partial nonclassical formulation for **24** should be preferable to the classical structure in order to explain the rapid conversion of **5** into **24**.

In summary then, the following facts emerge from the present study. (1) In spite of a structure designed to favor endo 3,2-methyl migration through providing an unusually stable ion as the immediate product of such rearrangement, the present research cannot demonstrate that no endo 3,2-methyl migration occurs. (2) If one agrees that such endo migration is unlikely, the initially formed carbonium ion rapidly achieves epimerization *via* Wagner–Meerwein rearrangement, 6,2-hydride migration, and Wagner–Meerwein rearrangement; and the resultant epimer rapidly affords the very stable anisylic ion *via* exo 3,2-methyl migration. (3) The anisylic ion, in concentrated sulfuric acid, rapidly equilibrates with its enantiomer without involving a cyclene, becoming racemic in ~2 min, incorporating but traces of deuterium in the methyl groups and none in the ring system, when formed from **20** in deuteriosulfuric acid. (4) Equivalence in deuterium distribution between the two alkyl–methyl groups of **21** formed from labeled **1** is explicable in terms of the same mechanism which accounts for racemization. (5) The remaining, though remote, possibility that such equivalence in deuterium labeling of the alkyl–methyl groups may be achieved *via* exo 3,2-*p*-anisyl migration is not presently answerable.

One may infer that in the substituted norbornyl cation there is at least some nonclassical character where the classical formulation requires a secondary carbonium ion in order to account for the facile intervention of such ions in the array of available rearrangement mechanisms.

## Experimental Section

Melting points, determined using a Thomas-Hoover or modified Hershberg apparatus, are uncorrected. Infrared data were obtained on a Perkin-Elmer Model 273B grating spectrophotometer. Ultraviolet and visible spectra were obtained on a Beckman Model DB spectrophotometer. The nmr data were obtained at 60 Mc using a Varian Associates Model A-60 nmr spectrometer and are expressed as shift downfield from internal tetramethylsilane in parts per million. The mass spectra were recorded on an Associated Electrical Industries Ltd. Model MS-

(31) P. D. Bartlett, C. E. Dills, and H. G. Richey, Jr., *J. Amer. Chem. Soc.*, **82**, 5414 (1960).

(32) C. H. Rochester in "Acidity Functions," Academic Press, New York, N. Y., 1970.

(33) See D. G. Farnam and G. Mehta, *J. Amer. Chem. Soc.*, **91**, 3256 (1969), and references cited therein.

12 mass spectrometer. Deuterium analyses were obtained from mass spectra recorded on an Associated Electrical Industries Ltd. Model MS-9 mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

**Preparation of the Nmr Samples Containing Tris(dipivalomethanato)europium(III).**[34]—The sample was prepared in the usual manner by dissolving 80–85 mg ($3.3 \times 10^{-4}$ mol) of **21** in 0.4 ml of deuteriochloroform. To this was added 40–45 mg ($0.6 \times 10^{-4}$ mol) of tris(dipivalomethanato)europium(III). Gentle heating on the steam bath facilitated dissolution of the slightly soluble reagent. The mole ratio of **21** to shift reagent was 0.17. The resulting solution was filtered through a small cotton plug directly into an nmr sample tube. TMS (2 drops) was added and the spectra were recorded. The reported integration areas represent the average of four determinations.

**Ethyl Anisylglyoxylate (7).**—Into a 1000-ml, three-neck flask equipped with a mechanical stirrer, reflux condenser, and addition funnel was placed dry methylene chloride (160 ml) under nitrogen. To this, with stirring and cooling, was added gradually 36.4 g (0.27 mol) of anhydrous aluminum chloride. To this all at once was added 25 g (0.2 mol) of ethyl oxalyl chloride, and with further stirring and cooling, 19.8 g (19.9 ml, 0.18 mol) of purified anisole in dry methylene chloride (50 ml) over a period of 45 min. This mixture was stirred at room temperature for 1.5 hr.

Ice water (300 ml) was added to the cooled reaction with *caution*. The large chunks of white precipitate which formed initially upon hydrolysis went into solution with stirring, which was continued for 30 min. The reaction mixture was transferred to a 1.0-l. separatory funnel, the organic layer was separated, and the aqueous layer was extracted with 50 ml of methylene chloride. The combined organic extracts were washed with 75 ml of water, 75 ml of 10% sodium carbonate, and 75 ml of water, dried (anhydrous magnesium sulfate), concentrated, and fractionally distilled, giving 30 g (79%) of the keto ester **7**: bp 125–128° (1.0 mm) [lit.[16] bp 178–179° (13 mm)]; ir (thin film) 1730 (ester C=O), 1675 (ketone C=O), 1600, 1215, and 1165 $cm^{-1}$.

**Diethyl 2-Anisyl-2-butenedioate (9).**—In a 250-ml flask equipped with a mechanical stirrer, thermometer, reflux condenser, and addition funnel was placed 3.6 g (6.3 g of a 57% mineral oil dispersion, 0.15 mol) of sodium hydride and dry benzene (50 ml) under nitrogen. To this stirred mixture was added dropwise over a 30-min period 33.7 g (0.15 mol) of triethyl phosphonoacetate. During the addition the temperature was maintained below 30° by cooling with an ice bath. The clear solution was then stirred at room temperature for 1 hr. To this was added dropwise over a period of 30 min 30 g (0.14 mol) of the keto ester **7**. Upon addition a yellowish, gummy precipitate formed around the walls of the reaction flask. After all the ketone was added, the flask was heated with a steam bath to 65–70° for 20 min and cooled to 15–20°, and the benzene was decanted. Additional benzene (50 ml) was added to the flask, which was heated to 70–75° with stirring and cooled to 15–20°; then the benzene was decanted. This procedure was repeated five times. (Alternatively, water could be added to dissolve the gummy precipitate and benzene used to extract in the normal fashion.) Concentration of the organic extracts at atmospheric pressure followed by distillation gave 39.5 g (90%) of the diester **9**: bp 145–160; ir (thin film) 1720 and 1735 (C=O), 1600, 1290, and 1176 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.16–1.46 (t, 6, $-CH_2CH_3$), 3.77 (s, 3, $-OCH_3$), 3.98–4.50 (q, 4, $-OCH_2CH_3$), 6.1 (s, 1, =CH), and 7.09 (q, 4, $J$ = 9 Hz, aromatic).

**2-Anisyl-2-butenedioic Acid (10).**—In a 250-ml flask was placed 32.5 g (0.12 mol) of the diester **9** in 95% ethanol (100 ml). To this with cooling was added 19.8 g (0.35 mol) of potassium hydroxide in water (75 ml). After refluxing for 1 hr, the solution was cooled and added to an equal volume of water. After the ethanol was removed *in vacuo*, the aqueous solution was extracted with 2 × 50 ml of ether, cooled in an ice bath, and acidified by the slow addition of concentrated sulfuric acid. The precipitate was collected and dried (phosphorus pentoxide) to yield 26.1 g (100%) of slightly yellow diacid **10**: mp 215–218°; ir (KBr) 1665 (C=O), 1595, 1225, and 1185 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 3.80 (s, 3, $-OCH_3$), 6.23 (s, 1, =CH), and 7.25 (q, 4, $J$ = 9 Hz, aromatic).

***p*-Anisylmaleic Anhydride (6).**—The diacid **10** (10.0 g, 0.045 mol) was intimately mixed with 6.82 g (0.05 mol) of phosphorus pentoxide. The mixture was transferred to a large sublimer and the sublimer was evacuated and immersed in an oil bath at 100°. The temperature was increased slowly and yellow crystals began collecting after 15 min. After subliming at 125–135° (0.4 mm) for 5–15 hr, the crystals were collected (sometimes more than one collection was necessary) and recrystallized from petroleum ether (bp 30–60°)–acetone to yield 5.6 g (60%) of the yellow anhydride **6**: mp 142–143.5° (lit.[15] mp 143–144°); ir (KBr) 1840 and 1760 (C=O), 1605, 1512, 1180, and 840 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 3.9 (s, 3, $-OCH_3$), 6.82 (s, 1, =CH), and 7.49 (q, 4, aromatic).

***exo*-2-*p*-Anisylnorbornane-*cis*,*endo*-2,3-dicarboxylic Acid (12).**—In a 250-ml, three-neck flask equipped with a magnetic stirrer, reflux condenser, and addition funnel was placed 6.9 g (0.03 mol) of the anhydride **6** in dry benzene (70 ml) and reagent acetone (56 ml) under nitrogen. To this all at once was added 5.6 g (6.9 ml, 0.085 mol) of freshly cracked cyclopentadiene. The mixture was stirred at room temperature for 21 hr and at 45–50° for 27 hr. After cooling, the organic solvents were removed *in vacuo* to yield a yellow oil.

The oil was added to a 500-ml flask in 95% ethanol (60 ml), and 12% aqueous potassium hydroxide (70 ml) was added. This mixture was refluxed for 12 hr and cooled, and the ethanol was removed *in vacuo*. The remaining aqueous layer was extracted with 2 × 50 ml of ether, treated with charcoal, and filtered to yield a slightly yellow solution.

The yellow solution was added to a 500-ml Parr hydrogenation bottle with 100 mg of 5% palladium on charcoal. After 8 min the theoretical amount of hydrogen had been absorbed. Hydrogenation was continued for 0.5 hr to ensure the completeness of the reaction. The mixture from hydrogenation was vacuum filtered through a layer of charcoal on top of a layer of Celite Filter-aid, and subsequently washed with small amounts of water. The resulting filtrate was added dropwise to a cooled (ice bath) solution of concentrated hydrochloric acid (30 ml) over a period of 45 min. After the addition, the precipitate was stirred for an additional 30 min, filtered and dried under vacuum (phosphorus pentoxide) to yield 8.9 g (92%) of the bicyclic diacid **12** as a white solid, mp 151–154°. Recrystallization from acetone gave an analytical sample: mp 155–156.5°; ir (KBr) 1700 (C=O), 1505, 1250, and 860 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 1.18–3.10 (complex m, bridgehead H and $CH_2$'s), 3.69 (s, 3, $-OCH_3$), 7.20 (q, 4, $J$ = 9 Hz, aromatic), and 11.9 (broad s, 1.5, $-COOH$).

*Anal.* Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.26. Found: C, 66.16; H, 6.22.

***exo*-2-*p*-Anisylnorborn-5-ene-*cis*,*endo*-2,3-dicarboxylic Acid (11).**—The unsaturated diacid **11** can be isolated by addition of the basic saponification solution from the previous experiment to concentrated hydrochloric acid with cooling and stirring. Further stirring, followed by collection and drying (phosphorus pentoxide) under vacuum, yielded the unsaturated diacid **11** as a white solid, mp 174–179° (lit.[35] mp 182.5–183.5°). Recrystallization from acetone gave an analytical sample: mp 187–188.5; ir (KBr) 1705 (C=O), 1520, 1225, and 850 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 1.3 (broad, s, 2, bridge $CH_2$), 2.88–3.68 (complex m, 3, bridgehead H and tertiary H), 3.72 (s, 3, $-OCH_3$), 6.29 (m, 2, =CH), 6.28 (q, 4, $J$ = 9 Hz, aromatic), and 12.7 (broad s, 1.9, $-COOH$).

*Anal.* Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.51; H, 5.63.

***exo*-2-*p*-Anisylnorbornane-*endo*-2,3-dicarboxylic Anhydride (13).**—In a 500 ml flask was placed 5.0 g (0.02 mol) of the diacid **12** in reagent acetic anhydride (210 ml). The mixture was stirred magnetically for 18 hr at room temperature. The excess acetic anhydride was removed after this time at 40–50° (2.0 mm) to yield a yellow oil. Distillation gave 4.06 g (88%) of the anhydride **13**: bp 172° (0.25 mm); ir (thin film) 1850 and 1775 (C=O), 1610, 1250, and 920 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.62 (m, 6, $CH_2$'s), 2.95 (m, 2, bridgehead H), 3.70 (m, 1, tertiary H), 3.79 (s, 3, $-OCH_3$), and 7.16 (q, 4, $J$ = 9 Hz, aromatic).

*Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.65; H, 5.97.

**Dimethylammonium *exo*-2-*p*-Anisyl-*endo*-3-(*N*,*N*-dimethylcarbamido)norbornane-*endo*-2-carboxylate (14).**—In a 500-ml, three-neck flask equipped with a Dry Ice condenser capped with a drying tube was placed 5.3 g (0.02 mol) of the anhydride **13** in dry benzene (10 ml) and dry ether (30 ml) under nitrogen. To this at −5° was added as quickly as possible 2.6 ml (1.8 g,

(34) Tris(dipivalomethanato)europium(III) purchased as Eu-resolve from Alfa Inorganics, Inc., Beverly, Mass., No. 87898.

(35) H. Ruus, Ph.D. Thesis, University of Illinois, 1957.

0.04 mol) of liquid dimethylamine. The yellow solution turned colorless instantaneously, and after 5 min a voluminous white precipitate filled the reaction vessel. This was stirred magnetically overnight, the Dry Ice condenser being allowed to spend itself naturally. The white precipitate was collected by suction filtration and washed with ether to yield 6.7 g (93%) of the dimethylammonium salt **14**: mp 135–140°; ir (KBr) 1640 (amide C=O), 1575 (carboxylate C=O), 1515, and 1250 $cm^{-1}$.

*Anal.* Calcd for $C_{20}H_{30}O_4N_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.34; H, 8.26; N, 7.69.

***exo*-2-*p*-Anisyl-*endo*-2-(hydroxymethyl)-*endo*-(*N*,*N*-dimethylamino)norbornane (15).**—In a 500-ml three-neck flask equipped with a mechanical stirrer, reflux condenser, and addition funnel was placed dry tetrahydrofuran (100 ml) under nitrogen. To this was added 4.4 g (0.12 mol) of lithium aluminum hydride with stirring and cooling. To this at 0° was added dropwise 4.2 g (0.012 mol) of the dimethylammonium salt **14** suspended in dry tetrahydrofuran (150 ml). After the addition was complete the mixture was refluxed for 10 hr and cooled to ice bath temperature, and 4.4 ml of water, 4.4 ml of 25% potassium hydroxide solution, and 13.2 ml of water were added in succession with *caution*. The white suspension was vigorously stirred at room temperature for 10 min and at reflux for 30 min. The solution was then cooled and filtered, the salts being washed several times with ether. The tetrahydrofuran was removed *in vacuo*, and the residue was taken up in ether, washed with water, dried (anhydrous magnesium sulfate), and concentrated to yield 13.2 g (82.5%) of the amino alcohol **15**, mp 75–92°. Recrystallization from heptane (3 g/75 ml) gave a sample with mp 80–85°. An analytical sample (four recrystallizations from heptane) had mp 97.5–99.5°: ir (KBr) 3200 (–OH), 2955, 2880, 1515, 1255, and 1045 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.0–1.6 (complex m, 6.9, $CH_2$'s), 2.3 (s, 6, $-NCH_3$), 2.5–3.8 (complex m, 7, $-CH_2N-$, bridgehead H, and tertiary H), 3.71 (s, 3, $-OCH_3$), and 7.13 (q, 4, $J$ = 9 Hz, aromatic).

*Anal.* Calcd for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.45; H, 9.34; N, 4.67.

***exo*-2-*p*-Anisyl-*endo*-2-(hydroxymethyl)-*endo*-(*N*,*N*-dimethylaminomethyl)norbornane Oxide (16).**—In a 100-ml flask equipped with a magnetic stirrer was placed 5.0 g (0.02 mol) of the amino alcohol **15** in reagent methanol (24 ml). To this at room temperature was added 4.50 ml (0.052 mol) of 30% hydrogen peroxide over a period of 3 min. After the solution was stirred for 60 hr, an additional 2.0 g (0.021 mol) of 30% hydrogen peroxide was added all at once, and stirring was continued. After a total of 120 hr, platinum black was added to destroy the excess hydrogen peroxide. After oxygen evolution had ceased, the mixture was filtered through Celite Filter-aid to remove the platinum black and concentrated *in vacuo* to yield a viscous oil which partially solidified on standing: ir (thin film) 1515, 1250, and 1030 $cm^{-1}$. At this point the amine oxide **16** was suitable for use in the following reaction. A picrate was prepared by treatment with ethanolic picric acid: mp 168–172°; ir (KBr) 3480 (–OH), 1625, 1560, 1320, and 720 $cm^{-1}$.

*Anal.* Calcd for $C_{24}H_{30}O_{10}N_7$: C, 53.93; H, 5.66; N, 10.48. Found: C, 53.58; H, 5.54; N, 10.37.

***exo*-2-*p*-Anisyl-*endo*-2-(hydroxymethyl)-3-methylenenorbornane (17).**—The crude amine oxide **16** from the previous reaction was placed in a 200-ml flask equipped with a distillation head and evacuated to 20 mm with a water aspirator. The flask and contents were immersed in an oil bath at 90° and the temperature was slowly increased. Decomposition and distillation of dimethylhydroxylamine commenced at 158°, and was finished after 15 min at 168°. The flask was maintained at 170° for an additional 10 min and cooled to room temperature, and the residue was taken up in ether. The ether solution was washed with 5% hydrochloric acid, 5% sodium bicarbonate, and water, dried (anhydrous magnesium sulfate), concentrated, and distilled, giving 2.76 g (64%) of the unsaturated alcohol **17**: bp 138° (0.1 mm); ir (thin film) 3400 (–OH), 3050 (=CH), 2950 (–CH), 1650 (C=C), 1510, 1250, 1040, and 830 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.87–2.10 (complex m, 7, $CH_2$'s and –OH), 2.5–2.8 (broad d, 2, bridgehead H), 3.60 (broad s, 2, $-CH_2O$), 3.70 (s, 3, $-OCH_3$), 4.77 and 5.15 (d, s, $=CH_2$), and 7.0 (q, 4, $J$ = 9 Hz, aromatic).

*Anal.* Calcd for $C_{16}H_{20}O_2$: C, 78.69; H, 8.25. Found: C, 78.85; H, 8.41.

***exo*-2-*p*-Anisyl-*endo*-2-formyl-3-methylenenorbornane (18).**—In a 1000-ml flask was placed 19.8 ml (19.4 g, 0.025 mol) of dry pyridine in dry methylene chloride (375 ml) under nitrogen. To this with magnetic stirring and cooling was added 12.3 g (0.123 mol) of chromium trioxide. After the solution was stirred at room temperature for 30 min, most of the chromium trioxide had dissolved and the solution was dark burgundy in color. To this all at once was added 5.0 g (0.021 mol) of unsaturated alcohol **17** in methylene chloride (5 ml). A black, gummy precipitate formed immediately. After stirring for 2 hr at room temperature, the solution was decanted and the residue was triturated with ether. To the combined organic layers was added an additional 500 ml of ether. The organic portion was washed with 3 × 100 ml of 5% sodium hydroxide, 100 ml of 5% hydrochloric acid, 100 ml of 5% sodium bicarbonate, and 100 ml of saturated sodium chloride, dried (anhydrous magnesium sulfate), and concentrated to yield a slightly colored oil which partially crystallized overnight. Distillation gave 4.05 g (81.7%) of the unsaturated aldehyde **18**: bp 127–130° (0.2 mm); ir (thin film) 3055 (=CH), 2950 (–CH), 1720 (C=O), 1650 (C=C), 1515, and 1250 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.98–1.8 (complex m, 6, $-CH_2$'s), 2.66–2.94 (broad d, 2, bridgehead H), 3.70 (s, 3, $-OCH_3$), 4.92 and 5.45 (d, 1.7, $=CH_2$), 7.01 (q, 4, $J$ = 9 Hz, aromatic), and 9.55 (s, 0.75, –CHO).

*Anal.* Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.34; H, 7.41.

***exo*-2-*p*-Anisyl-*endo*-2-formyl-3-methylenenorbornane Semicarbazone (19).**—In a 125-ml erlenmeyer flask, 4.05 g (0.017 mol) of the unsaturated aldehyde **18** was dissolved in 95% ethanol (40 ml). Water was added until cloudiness persisted and the ethanol was added to regenerate the clear solution. To this was added 3.54 g (0.032 mol) of semicarbazide hydrochloride and 5.45 g (0.04 mol) of sodium acetate trihydrate. After dissolution by swirling the mixture was heated on a steam bath for 5 min. The solution was cooled, and the white solid which separated was collected and dried (phosphorus pentoxide), giving 4.18 g (84.4%) of the unsaturated semicarbazone **19**: mp 197.5–201.5°; ir (KBr) 3455 (NH), 2955 (CH), 1695 (C=O), 1580 (C=N), 1510, and 1250 $cm^{-1}$.

*Anal.* Calcd for $C_{17}H_{21}O_2N_3$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.17; H, 7.01; N, 14.03.

***exo*-2-*p*-Anisyl-*endo*-2-methyl-3-methylenenorbornane (1) (Iso-*p*-anisylapocamphene).**—In a 15-ml flask was placed an intimate mixture of 1.0 g (0.0034 mol) of the unsaturated semicarbazone **19** and 657 mg (0.012 mol) of potassium hydroxide. The flask was fitted with a semimicro distillation apparatus and evacuated to 0.06 mm. Heating was applied by means of an oil bath and the temperature was increased. At 205–215° decomposition commenced and proceeded vigorously until 230°. Heating was maintained for an additional 10 min at 230° to ensure the completeness of the reaction. The yield of crude collected **1** was 686 mg (90%). This material was redistilled, giving 574 mg (75%) of **1**: bp 115–118° (0.08 mm); ir (thin film) 3055 (CH), 1650 (C=C), 1515, 1250, 1180, 1040, and 830 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.85–1.97 (broad m, $CH_2$'s), 1.38 (s, $-CH_3$), 2.32 and 2.75 (broad s, bridgehead H), 3.67 (s, 3, $-OCH_3$), 4.68 and 5.16 (d, 1.7 $=CH_2$), and 6.94 (q, 4, $J$ = 9 Hz, aromatic); nmr (concentrated $H_2SO_4$) $\delta$ 1.04–2.49 (complex m, 7, $CH_2$'s and $C_4$ H), 1.57 (broad s, 6, $-CH_3$'s), 4.16 (broad s, 1, CH), 4.19 (broad s, 3, $-OCH_3$), and 7.84 (m, 4, aromatic); nmr ($CF_3COOH$) $\delta$ 0.82–2.40 (complex m, 7, $CH_2$'s and $C_4$ H), 1.26 (2, 3, $-CH_3$), 1.29 (s, 3, $-CH_3$), 3.61 (broad s, 1, $C_1$ H), 3.89 (s, 3, $-OCH_3$), and 7.53 (m, 4, aromatic); uv max (concentrated $H_2SO_4$) 384.9 nm (log $\epsilon$ 4.68).

*Anal.* Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.31; H, 8.84.

***exo*-2-*p*-Anisyl-*endo*-2-(deuteriomethyl)-3-methylenenorbornane (1-$CH_3$-*d*).**—In a 15-ml flask was placed 1.23 g (0.011 mol) of potassium *tert*-butoxide and 0.21 g (0.21 ml, 0.01 mol) of deuterium oxide. These reacted within 15 min to yield a grayish, syrupy liquid. To this was added 1.0 g (0.0034 mol) of the unsaturated semicarbazone **19**. Manual mixing with a spatula ensured the wetness of the solid semicarbazone. The flask was fitted with a semimicro distillation apparatus and the system was evacuated to 0.14 mm. Heating was applied with an oil bath and the temperature was increased. Decomposition began at 215° and continued through 250°. The yield of crude collected 1-$CH_3$-*d* was 671 mg (88%). Redistillation gave 491 mg (65%) of the colorless 1-$CH_3$-*d*: bp 115–127° (0.08 mm); ir (thin film) 3055 (CH), 2950 (CH), 1650 (C=C), 1520, 1250, 1180, and 830 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 0.88–1.96 (complex m, $-CH_2$'s), 1.38 (broad s, $-CH_3$-*d*), 2.35 and 2.79 (broad s, 2, bridgehead H), 3.78 (s, 3, $-OCH_3$), 4.71 and 5.21 (d, 1.8, $=CH_2$),

and 7.09 (q, 4, $J$ = 9 Hz, aromatic). The nmr spectra displayed a considerable reduction of the methyl singlet while other portions of the spectra remained constant.

*exo*-2-*p*-Anisyl-3,3-dimethyl-*endo*-2-norbornanol (20) (*p*-Anisylcamphenilol).—Alcohol **20** was prepared by the method of Bartlett, *et al.*, from (−)-camphenilone: mp 138–140° (lit.[12] mp 143.5–144.5°); $[\alpha]_D$ −24.72° (c 6.22 benzene) [lit.[12] $[\alpha]_D$ −25.7° (c 4.2, benzene)]; nmr (concentrated $H_2SO_4$) δ 1.3–2.9 (complex m, $CH_2$'s) and $C_4H$), 1.72 (broad s, 6, $-CH_3$'s), 4.35 (broad s, $C_1$ H), 4.37 (broad s, $-OCH_3$), and 8.02 (m, aromatic); uv max (concentrated $H_2SO_4$) 385.2 nm (log ε 4.6).

*endo*-2-*p*-Anisyl-*exo*-methyl-3-methylenenorbornane (2) (*p*-Anisylapocamphene).—Olefin **2** was prepared according to the procedure of Bartlett, *et al.*:[12] nmr ($CDCl_3$) δ 0.85–2.00 (complex m, $CH_2$'s), 1.38 (s, 3, $-CH_3$), 2.22 and 2.75 (m, 2, bridgehead H), 3.65 (s, 3, $OCH_3$), 4.65 and 5.10 (d, 2, $=CH_2$), and 6.99 (q, 4, aromatic).

**Carbonium Ion Trapping Experiments.** *endo*-2-*p*-Anisyl-3,3-dimethyl-*exo*-2-norbornanol (21) (Iso-*p*-anisylcamphenilol). **A. General Procedure.**—The starting substrate (450–550 mg) was dissolved in concentrated sulfuric acid or deuteriosulfuric acid by swirling. The resulting orange solution was allowed to stand at room temperature for the specified time. This was then rapidly and with stirring poured into 200 ml of ice water, and the resulting aqueous solution was extracted with 2 × 100 ml of ether. The ether extracts were combined and washed with 100 ml of 5% sodium bicarbonate and 100 ml of saturated sodium chloride, dried (anhydrous magnesium sulfate), and concentrated to yield a yellow oil which crystallized after standing at room temperature for several hours. Two recrystallizations from heptane yielded white needles of **21**. The physical constants found for **21** from the various starting substrates are listed in Table III.

TABLE III
PHYSICAL CONSTANTS FOR 21 ISOLATED FROM VARIOUS STARTING MATERIALS

| Substrate | Acid | Time, min | Mp, °C | $\alpha^{26.0}D$ |
|---|---|---|---|---|
| **20** | $H_2SO_4$ | 30 | 77.4–78.4 | |
| **2** | $D_2SO_4$ | 10 | 77.0–78.5 | |
| **1** | $D_2SO_4$ | 10 | 74.5–75.5 | |
| **20** | $D_2SO_4$ | 10 | 79.0–79.5 | |
| 1-$CH_3$-*d* | $H_2SO_4$ | 10 | 71.0–74.5 | |
| (−)-**20** | $H_2SO_4$ | 2 | 79.0–79.5 | −0.10° |
| (−)-**20** | $H_2SO_4$ | 21 | 79.0–80.5 | −0.08° |
| (−)-**20** | $H_2SO_4$ | 30 | 77.8–79.5 | |

**B. Specific Procedure.**—The alcohol **20** (1.0 g, 0.04 mol) was dissolved in 10 ml of concentrated sulfuric acid by swirling. The orange solution, after standing at room temperature for 30 min, was poured into 200 ml of ice water with stirring. The aqueous mixture was extracted with 2 × 100 ml of ether, and the ether extracts were combined and washed with 100 ml of 5% sodium bicarbonate and 100 ml of saturated sodium chloride, dried (anhydrous magnesium sulfate), and concentrated to yield a yellow oil which solidified after standing at room temperature for 2 hr to give 820 mg (82%) of crude **21**, mp 66–76°. Recrystallization from 10 ml of hot heptane gave 478 mg (48%) of **21** as white needles: mp 77.4–78.4° (lit.[12] mp 76–78°); ir (KBr) 3455 (–OH), 2940 (CH), 1515, and 1245 $cm^{-1}$; nmr ($CDCl_3$) δ 0.80 (s, 3, $-CH_3$), 1.10–1.90 (complex m, $CH_2$'s and –OH), 1.29 (s, $-CH_3$), 2.15–2.63 (complex m, 2, bridgehead H), 3.79 (s, 3, $-OCH_3$), and 7.10 (q, 4, $J$ = 9 Hz, aromatic); nmr [$CDCl_3$ and Eu(DPM)$_3$] δ 1.68 (s, 3, $-CH_3$), 1.76–2.76 (complex m, 6, $CH_2$'s), 3.18 (s, 3, $-CH_3$), 3.50 (s, 1, –OH), 3.88 (s, 3, $-OCH_3$), 4.34–4.98 (m, 2, $C_1$ H and syn 7-H), and 7.80 (q, 4, aromatic).

*Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.99; H, 8.94.

**Registry No.**—**1**, 36004-27-0; 1-$CH_3$-*d*, 36004-28-1; **9**, 36004-29-2; **10**, 36004-30-5; **11**, 36004-31-6; **12**, 36004-32-7; **13**, 36004-33-8; **14**, 36004-34-9; **15**, 36004-35-0; **16** picrate, 36004-36-1; **17**, 36004-37-2; **18**, 36015-21-1; **19**, 36004-38-3; **21**, 22551-05-9.

**Acknowledgments.**—One of us (D. L. A.) wishes to acknowledge the following generous support:[2] Esso Education Foundation Fund (summers 1967–1970), University of Connecticut Graduate Assistants' Summer Fellowship, 1971. The high-resolution mass spectral deuterium analyses were made possible by an instrument grant from the National Science Foundation, NSF GP-18332, and the authors are indebted to Professor Robert B. Fairweather of this department for his assistance in collecting and interpreting the data. Finally the authors are indebted to Professor Paul D. Bartlett, Harvard University, for making available various unpublished spectrographic data relative to **1** and **2**.

# Hydrogenation of 9,10-Dimethylanthracene with Cobalt Hydrocarbonyl

PAUL D. TAYLOR AND MILTON ORCHIN*

*Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221*

*Received May 23, 1972*

The hydrogenation of 9,10-dimethylanthracene can be achieved with cobalt hydrocarbonyl at room conditions. Although the product consists of a mixture of *cis*- and *trans*-9,10-dihydro-9,10-dimethylanthracenes, a mechanism consistent with exclusive cis addition is suggested.

The catalytic homogeneous hydrogenation of a variety of polynuclear hydrocarbons is reported[1] to proceed smoothly in the presence of $Co_2(CO)_8$ and synthesis gas (CO + $H_2$) at elevated temperatures and pressures. The hydrogenation is reported to be quantitative and to lead exclusively to dihydro and tetrahydro products. With anthracene, for example, 9,10-dihydroanthracene is the sole product. Since under these reaction conditions the catalytic species is unquestionably $HCo(CO)_4$, or $HCo(CO)_3$ with which it is in equilibrium, it was of interest to learn whether such aromatic compounds could be reduced at room conditions with stoichiometric quantities of $HCo(CO)_4$. We have now found that such is the case; *e.g.*, 9,10-dimethylanthracene (**1**) is converted essentially completely into the corresponding 9,10-dihydro derivative. This reaction provided a further opportunity to study the stereochemistry of $HCo(CO)_4$ reactions. Although the stereochemistry of the hydroformylation of olefins has not been ascertained conclusively, the hydrogenation[2] and the isomerization[3] of olefins with $HCo(CO)_4$

(1) S. Friedman, S. Metlin, A. Svedi, and I. Wender, *J. Org. Chem.*, **24**, 1287 (1959).

(2) W. L. Fichtenan and M. Orchin, *ibid.*, **33**, 1281 (1968).

(3) F. Piacenti, S. Pucci, M. Bianchi, R. Lazzaroni, and P. Pino, *J. Amer. Chem. Soc.*, **90**, 6847 (1968); R. Casey and C. Cyr, *ibid.*, **93**, 1280 (1971), P. Taylor and M. Orchin, *ibid.*, **93**, 6504 (1971).

have been shown to proceed *via* a cis process. In the present study we have found that the reduction of **1** with $HCo(CO)_4$ leads to a mixture of *cis*- and *trans*-9,10-dihydro products **2** and **3**; however, as will be shown, this fact is not necessarily inconsistent with exclusive cis addition.

## Experimental Section

**Analysis.**—Analysis of the products from the reaction with anthracene and with **1** was performed on an F & M gas chromatograph equipped with a 10 ft × $^1/_{16}$ in. stainless steel column packed with silicone XE-60 (5 wt %) supported on Ana-Chrome ABS 90–120 mesh using helium (38 ml/min) as the carrier gas. At a column temperature of 200°, 9,10-dihydroanthracene is eluted before anthracene, and *cis*-9,10-dihydro-9,10-dimethylanthracene (**2**) is eluted before the trans compound, **3**. After **2** and **3** were eluted, the column was programmed to 250° at 30° min to elute **1**. Concentrations were determined by measuring the peak areas by the method of triangulation. No other products, other than those reported, were detected.

**Materials.**—Anthracene (Matheson Coleman and Bell) was recrystallized three times from acetone and dried under vacuum (1 mm) for 4 hr at 25°, mp 220–222° (uncor). 9,10-Dimethylanthracene (Aldrich-Puriss. Grade) was used without further purification, mp 175–179° (uncor). Reagent grade benzene was dried over a molecular sieve before use. Tri-*n*-butylphosphine (Carlisle Chemical Co.) was vacuum-distilled and stored under nitrogen at −20°. $Co_2(CO)_8$ was prepared in the usual way.[4] The crystalline carbonyl was collected and stored at −20° under a carbon monoxide atmosphere. Synthesis gas was prepared by mixing equal amounts of carbon monoxide and hydrogen.

**Catalytic Hydrogenations.**—The catalytic hydrogenations were carried out in 30-ml, well-agitated high-pressure vessels. The catalyst was weighed accurately and placed in the reactor, which was then purged with CO, and 10 ml of a benzene solution of anthracene or **1** was added before sealing the vessel. The reactor was purged with carbon monoxide before pressuring with the desired amount of carbon monoxide and hydrogen. The reactors were heated (30 min) to the reaction temperature with agitation, kept at this temperature (±2°) for a specified period of time, and cooled (45 min) to room temperature before releasing the pressure. The solutions were withdrawn and analyzed by vpc.

A solution of 15.4 mg of **1** in 10 ml of dry benzene was added to 27.8 mg of $Co_2(CO)_8$ and the solution treated with $H_2/CO$ (1:1) at 3000 psi and 150° for 90 min. Vpc of the solution indicated a 99% yield of a mixture consisting of **2** (48%) and **3** (52%). Similar treatment of anthracene gave a 99% yield of 9,10-dihydroanthracene.

A solution of 15.4 mg of **1** in 10 ml of dry benzene was added to 31.9 mg of $Co_2(CO)_8$ and 0.146 g of tributylphosphine and the solution treated at 1600 psi and 150° for 90 min. Vpc of the solution indicated a 68% yield of a mixture consisting of **2** (44%) and **3** (56%).

A solution of 20.6 mg of **2** (containing 4% **3** as impurity) in 10 ml of dry benzene was added to 17.9 mg of $Co_2(CO)_8$ and the solution treated at 3000 psi and 150° as above. Vpc indicated a mixture of **2** (94%) and **3** (6%).

**Stoichiometric Hydrogenations with Cobalt Hydrocarbonyl.**—$HCo(CO)_4$ was prepared as described in the literature.[5] Its concentration was determined by addition of excess standardized NaOH solution and back titration with HCl using phenolphthalein as an indicator. Anthracene (or 9,10-dimethylanthracene) was dissolved in the appropriate solvent and treated with a solution of $HCo(CO)_4$ at 25° under an atmosphere of CO. The reaction mixture was worked up by adding 3 ml of dimethylformamide (DMF) to 10 ml of the product solution and stirring the mixture until the $Co_2(CO)_8$ color disappeared. Water (5 ml) was then added and the lower layer withdrawn using a syringe. The organic layer was washed twice with 5 ml portions of water and dried over $Na_2SO_4$ before analyzing by vpc.

A 20-ml solution of toluene containing 6.8 mmol of $HCo(CO)_4$ was added with stirring to 200 mg (1.12 mmol) of anthracene dissolved in 20 ml of toluene in a round bottom flask purged with carbon monoxide. The solution was stirred for 24 hr before being worked up as described above. Vpc indicated a 25% yield of 9,10-dihydroanthracene.

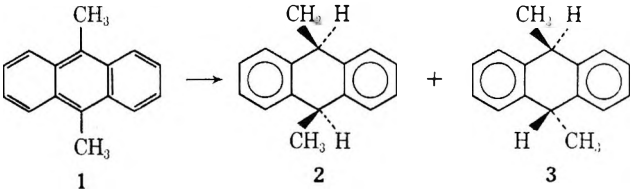
A 10-ml solution of toluene containing 4.74 mmol of $HCo(CO)_4$ was added with stirring to 46.4 mg of **2** dissolved in 20 ml of toluene as described above. The solution was stirred for 48 hr. Vpc of the solution indicated a 99% yield of a mixture consisting of **2** (35%) and **3** (65%).

A solution of 1.06 g of 1,1-diphenylethylene (Eastman) in 15 ml of pentane (spectroscopy grade) was injected into a 50-ml round bottom flask previously purged with CO. Then 10 ml of a cold solution of pentane containing 5.9 mmol of $HCo(CO)_4$ was injected into the flask with stirring. Within 10 min the solution turned dark, and after 1 hr it was very dark. The solution was stirred for 12 hr and then treated with 3 ml of DMF. The solution was washed three times with 5-ml portions of water, and the pentane layer was dried over sodium sulfate and then evaporated on a rotovap at 25°. The resulting liquid was analyzed by nmr and found to be 99% 1,1-diphenylethane.

A pentane solution containing 2.0 g of *cis*-stilbene was treated with 3 ml of a solution of pentane containing 5.91 mmol of $HCo(CO)_4$. The solution was stirred for 60 hr at 26° and worked up as above. The liquid product was analyzed by nmr spectroscopy and found to consist of 7% *trans*-stilbene, about 2% 1,2-diphenylethane, and 91% of unchanged material.

## Results and Discussion

The reduction of **1** gives a mixture of **2** and **3**, respectively. The mixture which results under various




oxo conditions is shown in Table I. That the cis isomer is not a precursor to the trans isomer was shown when the cis isomer was treated under catalytic oxo conditions with $Co_2(CO)_8$ and it was found to be inert to such treatment.

TABLE I
REDUCTION OF 9,10-DIMETHYLANTHRACENE (1)

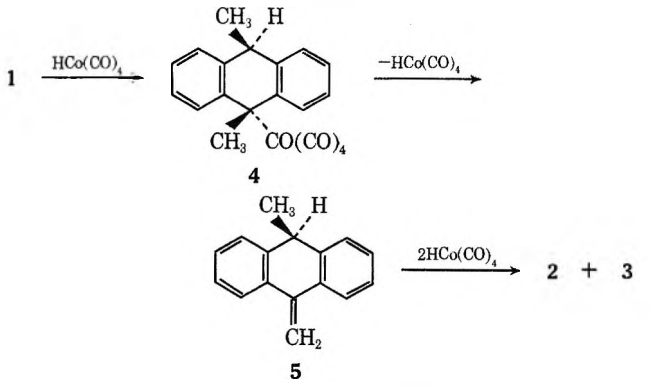
| Catalyst | Temp, °C | % cis (2) | % trans (3) |
|---|---|---|---|
| $Co_2(CO)_8$ | 150 | 48 | 52 |
| $Co_2(CO)_6(Bu_3P)_2$ | 150 | 44 | 56 |
| $HCo(CO)_4$ | 25 | 35 | 65 |

Addition to anthracene is usually thought to proceed by 1,4-conjugate addition at the meso positions. If addition of the H and $Co(CO)_4$ moieties occurs simultaneously, or if addition of the two moieties is from the same side, cis product should be formed exclusively. Most of the available evidence dealing with reactions of $HCo(CO)_4$ indicate that the addition is simultaneous. The failure to obtain cis product exclusively in the hydrogenation of **1** leads us to propose Scheme I. This scheme requires that compound **5** be present, at least at low concentration, as free olefin so that subsequent attack of $HCo(CO)_4$ can occur at either face of the olefin and thus produce both cis and trans isomers. This scheme also requires that the hydrogenolysis of **4** proceed slowly enough to permit competitive elimination to **5**. It is, of course, not necessary that the reaction of **5** with $HCo(CO)_4$ produce **4** again; anti-

(4) I. Wender, H. W. Sternberg, S. Metlin, and M. Orchin, *Inorg. Syn.*, **5**, 190 (1957).

(5) L. Kirch and M. Orchin, *J. Amer. Chem. Soc.*, **80**, 4428 (1958).

SCHEME I

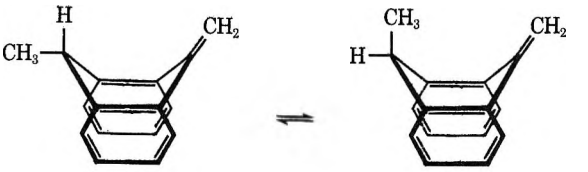



Markovnikov addition is also possible. In an experiment with the structurally related 1,1-diphenylethene, it was shown that the reaction proceeds smoothly and relatively rapidly with $HCo(CO)_4$ to give 1,1-diphenylethane. It is likely that this reaction proceeds by anti-Markovnikov addition

$$Ph_2C{=}CH_2 \longrightarrow Ph_2CHCH_2Co(CO)_4 \longrightarrow Ph_2CHCH_3$$

The reaction with **5** may proceed similarly. Preliminary results with $DCo(CO)_4$ showed, as expected, the presence of $D_3$ in both **2** and **3**. However, in addition to $D_3$ (~10%), there was substantial $D_1$ and $D_2$ present; the deuterium experiments are not clear-cut and need further investigation.

At this time we have no firm explanation for the differences in cis/trans ratio found under the different conditions shown in Table I. The intermediate **5**, if indeed it does exist, may be present in isomeric[6] form




**5a** **5b**

The equilibrium concentration of these isomers may change with temperature and the ratio of exo/endo attack by $HCo(CO)_4$ may be different for each isomer and also be affected by temperature.

**Registry No.**—**1**, 781-43-1; **2**, 13417-34-0; **3**, 13417-35-1; cobalt hydrocarbonyl, 16842-03-8.

**Acknowledgment.**—The authors are grateful to the Houdry Process and Chemical Division of Air Products and Chemicals, Inc., for generous support of this research in the form of a fellowship to Paul D. Taylor. Compound **2** was kindly furnished by Dr. David Morgan.

(6) S. J. Cristol, *Accounts Chem. Res.*, **4**, 393 (1971).

# The Polar and Steric Substituent Constants for an Alkylperoxy Group and Related Ether Groups

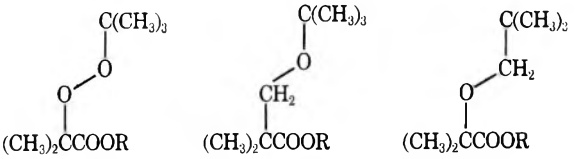
W. H. RICHARDSON,* R. S. SMITH, G. SNYDER, B. ANDERSON,[1] AND G. L. KRANZ

*Department of Chemistry, California State University, San Diego, San Diego, California 92115*

*Received May 3, 1972*

Rates of acid-catalyzed esterification were measured for 2-*tert*-butylperoxy-2-methylpropanoic acid (**1a**), 2,2-dimethyl-3-*tert*-butoxypropanoic acid (**2a**), and 2-methyl-2-neopentoxypropanoic acid (**3a**). Rates of the basic hydrolysis of the methyl esters of these acids were obtained and from the kinetic data from these two types of reactions $\sigma^*$ and $E_s$ values were calculated. The $\sigma^*$ and $E_s$ values for the substituents $(CH_3)_3COOC(CH_3)_2$, $(CH_3)_2COCH_2C(CH_3)_2$, and $(CH_3)_3CCH_2OC(CH_3)_2$ are +0.520 and −1.96, −0.166 and −1.57, and +0.178 and −1.43, respectively. These values are discussed with relationship to each other and to analogous groups that are reported in the literature. The basic hydrolysis of methyl 2-*tert*-butylperoxy-2-methylpropanoate (**1b**) yields *tert*-butyl alcohol and acetone. The origin of these fragmentation products is discussed by considering the rate of *tert*-butyl alcohol formation from **1b**, the rate of disappearance of **1b**, and the rate of disappearance of ethyl 2-*tert*-butylperoxy-2-methylpropanoate (**5**) in 85% ethanol. The basic hydrolysis of **1b** was considered as a possible source of excited-state carbonyl products. However, the lack of light emission from an acceptor (fluorescein) added to the reaction mixture indicates that excited-state carbonyl species are not produced.

As part of a program to evaluate neighboring peroxide group reactions[2] it was necessary to determine the polar substituent constant[3,4] $\sigma^*$ for an alkylperoxy group. To our knowledge there are no previous reports of such a substituent constant. Polar substituent constants for stereochemically similar ether groups were required as well and they are reported here. The $\sigma^*$ values were obtained from the rates of acid-catalyzed esterification of 2-*tert*-butylperoxy-2-methylpropanoic acid (**1a**), 2,2-dimethyl-3-*tert*-butoxypropanoic acid (**2a**), and 2-methyl-2-neopentoxypropa-




**1a**, R = H **2a**, R = H **3a**, R = H
**b**, R = $CH_3$ **b**, R = $CH_3$ **b**, R = $CH_3$

(1) National Science Foundation Undergraduate Research Participant, summer, 1969.

(2) (a) W. H. Richardson and V. F. Hodge, *J. Amer. Chem. Soc.*, **93**, 3996 (1971); (b) W. H. Richardson, J. W. Peters, and W. P. Konopka, *Tetrahedron Lett.*, 5531 (1966).

(3) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(4) We have retained the $\sigma^*$ symbol for convenience in estimating our neighboring peroxide group rate data, which will be reported later. It has been suggested that the $\sigma^*$ constant should be replaced by other substituent constants such as $\sigma_I$[5] and field and resonance constants.[6]

(5) C. D. Ritchie and W. F. Sager, "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Jr., Ed., Interscience, New York, N. Y., 1964, p 323.

(6) C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

noic acid (**3a**) in methanol and from the rates of the basic hydrolysis of the corresponding methyl esters (**1b**, **2b**, **3b**) in 85% ethanol. Since fragmentation products result from the basic hydrolysis of **1b**, our interest in these reactions[7] led to a study of the mechanism of this reaction.

The rates of esterification of the acids were measured by the same procedures that were employed previously.[8] The kinetic data must be treated to account for the formation of water in the esterification reaction. For hydrogen chloride catalyzed esterification (as used here), the derived rate coefficient is given in eq 1, where $a$ = initial carboxylic acid concentration, $x$ = concentration of ester formed at time $t$, and $r$ = a constant which is defined by eq 2. For esterification in methanol R in eq 2 is $CH_3$ and values of $r$ are temperature dependent and they are reported[8a,b] to be 0.11 at 0°, 0.20 at 20°, 0.25 at 30°, 0.32 at 40°, and 0.42 at 50°. We have used the reported $r$ value at 30° and processed the data with a least-squares computer program to give the rate coefficients that are shown in Table I. Acetic acid was included in our measurements in order to ensure a self-consistent set of data and it is in reasonable agreement with the value of $81.4 \times 10^{-3}$ l. mol$^{-1}$ sec$^{-1}$ reported by Smith.[8b] Since relative rate coefficients will be used to calculate substituent constants, this small discrepancy will not be troublesome. Data for the basic hydrolysis of esters **1b**, **2b**, **3b**, and methyl acetate are given in Table II. Since the peroxy-substituted ester **1b** yields the fragmentation products *tert*-butyl alcohol, acetone, and carbon dioxide (as carbonate), the titrimetric method that was used for the other esters could not be employed. For this reason, the overall rate of hydrolysis of **1b** was determined by following the appearance of *tert*-butyl alcohol by gas–liquid chromatography (glc).

$$k = \frac{(r + a) \ln \left(\frac{a}{a - x}\right) - x}{[\mathrm{HCl}]rt} \quad (1)$$

$$r = \frac{[\mathrm{ROH_2^+}][\mathrm{H_2O}]}{[\mathrm{H_3O^+}]} \quad (2)$$

TABLE I

KINETIC DATA FOR THE HYDROGEN CHLORIDE[a] CATALYZED ESTERIFICATION OF CARBOXYLIC ACIDS IN METHANOL AT 30.00°

| Acid | [Acid], $M$ | $10^3k$,[b] l. mol$^{-1}$ sec$^{-1}$ |
|---|---|---|
| $CH_3COOH$ | 0.486 | 71.6 ± 0.6 |
| | 0.510 | 72.3 ± 0.9 |
| | | Av 72.0 ± 0.4 |
| **1a** | 0.505 | 0.799 ± 0.005 |
| **2a** | 0.505 | 1.91 ± 0.02 |
| | 0.452 | 1.95 % 0.03 |
| | | Av 1.93 ± 0.02 |
| **3a** | 0.448 | 2.77 ± 0.03 |
| | 0.448 | 2.65 ± 0.02 |
| | | Av 2.71 ± 0.06 |

[a] [HCl] = 0.00706 $M$. [b] Individual rate coefficients are given with probable error and average values with average error.

TABLE II

KINETIC DATA FOR THE BASIC HYDROLYSIS OF ESTERS IN 85% AQUEOUS ETHANOL AT 25.00°

| Ester | $10^2$[Ester], $M$ | $10^2$[OH$^-$], $M$ | $10^3k$,[a] l. mol$^{-1}$ sec$^{-1}$ |
|---|---|---|---|
| $CH_3COOCH_3$[b] | 2.30 | 4.65 | 8.46 ± 0.08 |
| | 2.72 | 4.65 | 8.67 ± 0.08 |
| | 2.81 | 4.65 | 8.26 ± 0.05 |
| | | Av | 8.46 ± 0.14 |
| **1b**[c] | 4.52 | 41.5 | 1.86 ± 0.06 |
| | 4.58 | 48.2 | 1.82 ± 0.09 |
| | | Av | 1.84 ± 0.02 |
| **2b**[b] | 1.49 | 6.07 | 0.0907 ± 0.0022 |
| | 1.55 | 6.07 | 0.0853 ± 0.0029 |
| | | Av | 0.0880 ± 0.0027 |
| **3b**[b] | 1.39 | 6.08 | 0.890 ± 0.012 |
| | 1.45 | 6.08 | 0.887 ± 0.016 |
| | 1.85 | 6.08 | 0.873 ± 0.021 |
| | | Av | 0.883 ± 0.007 |

[a] Individual and average rate coefficients are given with probable and average error, respectively. [b] Titrimetric data. [c] Glc data by following the appearance of *tert*-butyl alcohol. Calculated from the pseudo-first-order rate coefficient by $k = k_\psi/[\mathrm{OH^-}]$.

Polar substituent constants were calculated from the data in Tables I and II with the well-known equation (eq 3)[3] for $\sigma^*$. These values, along with the steric substituent constants [$E_s \equiv \log (k/k_0)_A$], are given in Table III. The $\sigma^*$ values given in Table III are not directly comparable to reported values for similar groups. In order to make more direct comparisons, we have used the additivity principle[9] to convert the C-$(CH_3)_2$ terminus of the groups in Table III to a $CH_2$ terminus. Thus, by the additivity principle, $\sigma^*$ [$(CH_3)_3CCH_2OCH_2$] = $\sigma^*$ [$(CH_3)_3CCH_2OC(CH_3)_2$] − $2\sigma^*$ ($CH_3CH_2$) = 0.378. The smaller value of $\sigma^*$ [$(CH_3)_3CCH_2OCH_2$], compared to $\sigma^*$ ($CH_3OCH_2$) (0.520),[3] is not unreasonable considering the approximate calculation and the observation that substituent effects are transmitted through oxygen as seen by $\sigma^*$ ($C_6H_5OCH_2$) = 0.850[3] *vs.* $\sigma^*$ ($CH_3OCH_2$) = 0.520. This latter effect can be seen again in the comparison of the $\sigma^*$ values of $(CH_3)_3CCH_2OC(CH_3)_2$ and $(CH_3)_2$-$COCH_2C(CH_3)_2$ in Table III. For convenience of comparison, the *gem*-dimethyl terminus is converted to a methylene terminus by the additivity principle, where $\sigma^*$ [$(CH_3)_3CCH_2OCH_2$] = 0.378 and $\sigma^*$ [$(CH_3)_3$-$COCH_2CH_2$] = 0.034. If a fall-off factor of 0.34[9,10] is

$$\sigma^* = \frac{1}{2.48} [\log (k/k_0)_B - \log (k/k_0)_A] \quad (3)$$

TABLE III

POLAR AND STERIC SUBSTITUENT CONSTANTS CALCULATED FROM ACID-CATALYZED ESTERIFICATION OF CARBOXYLIC ACIDS AND BASIC HYDROLYSIS OF ESTERS

| Substituent | $\sigma^*$ | $E_s$ |
|---|---|---|
| $(CH_3)_3COOC(CH_3)_2$ | +0.520 | −1.96 |
| $(CH_3)_3COCH_2C(CH_3)_2$ | −0.166 | −1.57 |
| $(CH_3)_3CCH_2OC(CH_3)_2$ | +0.178 | −1.43 |

(7) (a) W. H. Richardson and R. S. Smith, *J. Amer. Chem. Soc.*, **89**, 2230 (1967); (b) *ibid.*, **91**, 3610 (1969); (c) W. H. Richardson and T. C. Heesen, *J. Org. Chem.*, **37**, 3416 (1972).

(8) (a) K. L. Loening, A. B. Garrett, and M. S. Newman, *J. Amer. Chem. Soc.*, **74**, 3929 (1952); (b) H. A. Smith, *ibid.*, **61**, 254 (1939); (c) H. Goldschmidt, H. Haaland, and R. S. Melbye *Z. Phys. Chem.* (*Leipzig*), **143**, 278 (1929); (d) H. Goldschmidt and R. S. Melbye, *ibid.*, **143**, 139 (1929); (e) H. Goldschmidt and A. Thuesen, *ibid.*, **81**, 30 (1912); (f) H. Goldschmidt and O. Udby, *ibid.*, **60**, 728 (1907).

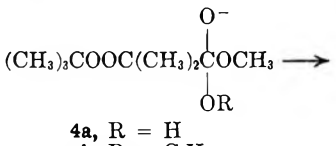
(9) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 224.

(10) This is the most common value for the fall-off factor, but other values have been suggested.[11]

(11) J. C. McGowan, *J. Appl. Chem.*, **10**, 312 (1960).

used, one predicts $\sigma^*$ [$(CH_3)_3CCH_2OCH_2CH_2$] = 0.13 (0.34 × 0.378), which is significantly larger than the estimated 0.034 value for $\sigma^*$ [$(CH_3)_3COCH_2CH_2$], which differs by replacement of *tert*-butyl for neopentyl in the R portion of the alkoxy group (RO). Since polar effects of the R portion of the RO group are transmitted through oxygen and since *tert*-butyl is more electron-releasing than neopentyl,[12] a decrease in $\sigma^*$ from 0.13 for $(CH_3)_3CCH_2OCH_2CH_2$ to 0.034 for $(CH_3)_3COCH_2CH_2$ is not unreasonable. By the same reasoning, the values of $\sigma^*$ for $(CH_3)_3COOC(CH_3)_2$ (0.520) and $(CH_3)_3CCH_2OC(CH_3)_2$ (0.178) are in qualitative accord, since an electron-withdrawing R group in $ROC(CH_3)_2$ should cause $\sigma^*$ to be more positive. The values for the steric parameters ($E_s$) of $(CH_3)_3COCH_2C(CH_3)_2$ and $(CH_3)_3CCH_2OC(CH_3)_2$ appear reasonable compared to the $E_s$ value of −1.54 for $CH_3C(CH_3)_2$.[3] A formal interpretation of $E_s$ would suggest that the *tert*-butylperoxy group is larger than either the $(CH_3)_3COCH_2$ or $(CH_3)_3CCH_2O$ groups. However, such formal interpretation of $E_s$ values for groups, other than for hydrocarbon groups, may be unwarranted.[13,14]

Previously we found that the peroxy-substituted acid **1a** undergoes a fragmentation reaction with base to give quantitative yields of *tert*-butyl alcohol and acetone.[7a,b] The basic hydrolysis of the methyl ester of this acid (**1b**) also yields these products. Although basic hydrolysis of **1b** to the acid **1a** followed by fragmentation of **1a** would explain the products, it is possible that fragmentation could occur entirely from the tetrahedral intermediate **4** formed in the ester solvolysis.

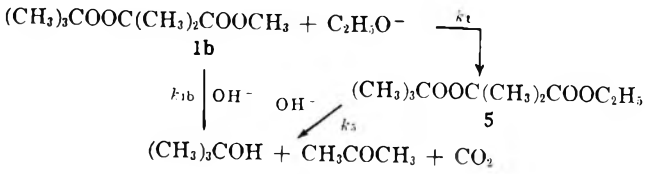


**4a**, R = H
**b**, R = $C_2H_5$

$$(CH_3)_3CO^- + CH_3COCH_3 + ROCOOCH_3 \quad (4)$$

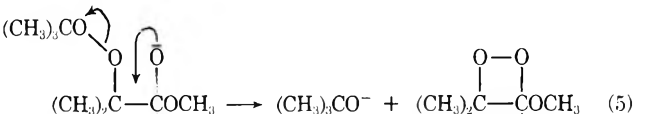
Analogous mechanisms were considered for the basic decomposition of α-hydroperoxy esters, but it was not determined which mechanism was operative.[15] Our data do not allow an unequivocal answer to this question, but we can state that eq 4 is not the exclusive reaction path for **4**. It is seen from Table II that the rate of *tert*-butyl alcohol formation ($k$ = 1.84 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$) is slower than the rate of methyl ester disappearance (Table IV) in the basic hydrolysis of **1b** in 85% ethanol. This can be explained by transesterification of **1b** to give the ethyl ester **5** in which **4b** is an intermediate, as shown in Scheme I. A steady-state

SCHEME I



treatment of this scheme gives $k_{1b} = k_B(1 + k_t/k_5R) - k_tR$ and $k_t = (k_5/k_B)k_{Me}(1/R + 1) - k_5 \cdot (1/R)$, where $R = [C_2H_5O^-]/[OH^-]$, $k_5$ = 0.996 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$ (the rate coefficient for disappearance of **5**), $k_B$ = 1.84 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$ (the rate coefficient for appearance of *tert*-butyl alcohol), and $k_{Me}$ = 3.58 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$ (the rate coefficient for the overall disappearance of **1b**). With $R \cong 2$ (calculated from the ionization constants of ethanol and water and accounting for the composition of the solvent),[16] the above two equations yield $k_{1b}$ = 5.93 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$ and $k_t$ = 2.41 × $10^{-3}$ l. $mol^{-1}$ $sec^{-1}$ so that the relative velocities, $v_{1b}/v_t = (k_{1b}/k_t)(1/R)$ = 1.2. The transesterification process is further verified by the glc observation that the ethyl ester **5** appears during the course of the basic hydrolysis of **1b**. Since transesterification proceeds through intermediate **4b**, it is clear that this intermediate does not undergo exclusively fragmentation by eq 4. This suggests that the intermediate in the basic hydrolysis of **1b** (*i.e.*, **4a**) does not undergo exclusively fragmentation either and thus *tert*-butyl alcohol and acetone arise in part from the basic fragmentation of the acid **1a**.

The possibility of generating excited-state carbonyl products from the basic hydrolysis of **1b** was pursued.[18] Providing that the intermediates are of sufficiently high energy, the resulting carbonyl products from **1b** could be produced in an excited state. Intermediates to consider are the carboxylate anion of **1a** and **4a** or **4b**. All of these intermediates can give carbonyl products, although this reaction was shown above not to be exclusive reaction path of the latter two species. Rather than directly producing carbonyl species from **4a** or **4b**, these intermediates could produce 1,2-dioxetanes (eq 5), which are known to undergo de-



**4** (R = H or $C_2H_5$) **6**

composition to produce excited-state carbonyl species.[19] To detect the presence of excited-state carbonyl species, fluorescein was used as an acceptor from which light emission can be detected.[2a] Under conditions where

TABLE IV

KINETIC DATA FOR THE RATE OF DISAPPEARANCE OF METHYL AND ETHYL 2-*tert*-BUTYLPEROXY-2-METHYLPROPANOATE DURING THE BASIC HYDROLYSIS IN 85% AQUEOUS ETHANOL AT 25.00°

| Ester | $10^2$[Ester], $M$ | [$OH^-$], $M$ | $10^3k$,[a] l. $mol^{-1}$ $sec^{-1}$ |
|---|---|---|---|
| **1b** | 5.12 | 0.451 | 3.64 ± 0.11 |
| | 5.12 | 0.452 | 3.52 ± 0.07 |
| | | | Av 3.58 ± 0.06 |
| **5** | 5.13 | 0.457 | 0.996 ± 0.022 |

[a] Individual rate coefficients are given with probable error. The average rate coefficient is given with average error. Glc data are used to obtain the rate coefficients.

(12) $\sigma^*$ ($t$-$C_4H_9$) = −0.300, $\sigma^*$ ($t$-$C_4H_9CH_2$) = −0.165.[3]
(13) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 42.
(14) K. Bowden, *Can. J. Chem.*, **44**, 661 (1966).
(15) M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **85**, 1655 (1963).
(16) $R = (K_a^{C_2H_5OH}/K_a^{H_2O})([EtOH]/[H_2O]) = (\sim 1)^{17}(2) = 2$.
(17) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960).
(18) See ref 7c for a similar consideration in the basic fragmentation of 2-*tert*-butylperoxy-2-methyl-1-propanol.
(19) See W. H. Richardson, M. B. Yelvington, and H. E. O'Neal, *J. Amer. Chem. Soc.*, **94**, 1619 (1972), and references cited therein.

light emission was detected from the basic decomposition of chloro-*tert*-butyl hydroperoxide (where 3,3-dimethyl-1,2-dioxetane is an intermediate) no light emission was detected from the basic hydrolysis of **1b** It may be concluded that **6** is not produced to a significant extent in this reaction and that other intermediates in the reaction are not of sufficiently high energy to give excited-state carbonyl products.

## Experimental Section[20]

Materials.—Methanol (ACS, reagent) was purified by refluxing over magnesium turnings with a catalytic amount of iodine followed by distillation.[21] The methanolic hydrogen chloride solution, used for acid-catalyzed esterification of the carboxylic acids, was prepared by bubbling anhydrous hydrogen chloride gas (Matheson) into methanol. The resulting solution was titrated with standard sodium hydroxide solution and the hydrogen chloride concentration was adjusted by adding the appropriate amount of methanol. The 85% ethanol was prepared by mixing 743.54 g of absolute ethanol (U.S. Industrial Chemicals, reagent grade) and 131.3 g of boiled distilled water. The stock base solution in 85% ethanol was prepared by mixing 1085 g of absolute ethanol, 185 g of boiled distilled water, and 8.00 g of carbonate-free 18 *M* sodium hydroxide solution. The resulting solution was stored in polyethylene bottles and periodically standardized against potassium acid phthalate to a phenolphthalein end point. The preparations of 2-*tert*-butylperoxy-2-methylpropanoic acid (**1a**) and 2-methyl-2-neopentoxypropanoic acid (**3a**) were described previously.[7b]

**Methyl 2-*tert*-Butylperoxy-2-methylpropanoate (1b).**—The acid **1a** (9.50 g, 54.0 mmol) was dissolved in 10 ml of ice-cold ether and treated with freshly generated diazomethane until the persistence of the yellow color of diazomethane indicated that all of the acid had undergone reaction. Diazomethane was prepared by adding dropwise a solution of 15.0 g (70.0 mmol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich Chemical Co.) in 100 ml of ether to 3.00 g of potassium hydroxide in a solution of 3.3 ml of water and 15 ml of 95% ethanol contained in the pot of a distilling apparatus, which was heated to 65°. The diazomethane distilled over with the ether into the receiver, which contained **1a**. After the reaction was completed, the ether was distilled at atmospheric pressure and then the product **1b** was distilled at 40° (1 mm), 6.48 g, 63% yield. The ir ($CCl_4$ solution) of **1b** showed the following significant absorptions: 2930, 1725, 1465, 1280, 1190, 1140, and 875 $cm^{-1}$. The nmr ($CCl_4$ solution) spectrum consisted of the following absorptions: $(CH_3)_3C$, 1.18, s, 9; $(CH_3)_2C$, 1.37, s, 6; and $COOCH_3$, 3.57, s, 3.

*Anal.* Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.53. Found: C, 57.02; H, 9.66.

**3-*tert*-Butoxy-2,2-dimethylpropanoic Acid (2a).**—3-*tert*-Butoxy-2,2-dimethylpropyl alcohol[22] (10.0 g, 63.0 mmol) was added dropwise to a stirred solution of chromium trioxide (20.0 g, 200 mmol) in 180 ml of acetic acid and 20 ml of water at room temperature. The solution was stirred for 12 hr, then diluted with 120 ml of water and extracted with five 20-ml portions of carbon disulfide. After drying over sodium sulfate, the carbon disulfide was allowed to evaporate, leaving 5.90 g (54% yield) of white crystals, mp 60.8–64.0°. These crystals of **2a** were sublimed three times at 70° (1 mm) and then dried under vacuum with phosphorus pentoxide for 2 days, mp 64.5–65.5° (5.30 g, 44% yield). The ir ($CCl_4$ solution) showed bands at 3400–3050 (broad), 2970–2860, 1700, 1475, 1250, 1200, 1090, 900, and 865 $cm^{-1}$. Absorptions in the nmr ($CCl_4$ solution) spectrum were observed at $(CH_3)_3C$ and $(CH_3)_2C$, 1.165 and 1.173, two singlets, 17; $CH_2$, 3.32, s, 2; and COOH, 12.0, s, 1.

*Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.22; H, 10.26.

**Methyl 3-*tert*-Butoxy-2,2-dimethylpropanoate (2b).**—This ester was prepared by the same procedure that was used for **1b**. The ir ($CCl_4$ solution) of the product, bp 69° (9 mm), showed the following absorptions: 2975, 1730, 1470, 1230, 1190, 1145, 1085, 965, and 895 $cm^{-1}$. The nmr ($CCl_4$ solution) spectrum was consistent with **2b**: $(CH_3)_3C$ and $(CH_3)_2$ 0.95, s, 15; $CH_2$, 3.26, s, 2; and $COOCH_3$, 3.62, s, 3.

*Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.70. Found: C, 63.70; H, 10.93.

**Methyl 2-Methyl-2-neopentoxypropanoate (3b).**—The diazomethane procedure described for **1b** was used to prepare **3b**, bp 30° (1 mm), in 92.5% yield. The ir ($CCl_4$ solution) spectrum showed absorptions at 2955, 1730, 1475, 1275, 1185, 1140, and 1080 $cm^{-1}$. The nmr ($CCl_4$ solution) assignments are $(CH_3)_3C$, 0.87, s, 9; $(CH_3)_2C$, 1.33, s, 6; $CH_2$, 2.95, s, 2; and $COOCH_3$, 3.67, s, 3.

*Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.70. Found: C, 63.48; H, 11.07.

**Ethyl 2-*tert*-Butylperoxy-2-methylpropanoate (5).**—A solution of 0.433 g (2.46 mmol) of **1a**, 0.1 ml of concentrated sulfuric acid, and 3 ml of absolute ethanol was allowed to reflux for 2.5 hr. The reaction mixture was neutralized with a 10% sodium bicarbonate solution and then 3 ml of water was added, followed by three 5-ml ether extractions. The combined ether extract was washed with 10% sodium bicarbonate solution and dried over magnesium sulfate, and the ether was removed by a rotevaporator. Distillation of the residue gave 0.331 g, bp 69–70° (6 mm), of **5**, 66% yield, which showed only one peak by glc analysis on a 5 ft × 0.125 in. 3% SE-30 on Varaport column at 60° with a nitrogen flow rate of 28 ml/min. The ir ($CCl_4$ solution) spectrum of **5** showed absorptions at 3055–2785, 1735, 1460, and 1360 $cm^{-1}$. The nmr ($CCl_4$ solution) spectrum was consistent with the structure of **5**: $(CH_3)_3C$, 1.24, s, 8.7; $(CH_3)_2C$, 1.40, s. 6.7; $COOCH_2CH_3$, 1.31, t, 3.1; and $COOCH_2CH_3$, 4.17, q, 2.0. The mass spectrum of **5** showed *m/e* 204 (M), 131 (M − $COOC_2H_5$), 57 [$(CH_3)_3C^+$].

**Kinetic Methods.**—The method of Smith[8b] was used to determine the rate of esterification of the acids with a catalytic amount of hydrogen chloride. A titrimetric method was used to determine the rates of the basic hydrolysis of all esters, except for the peroxy-substituted esters **1b** and **5**. The titrimetric method consisted of thermally equilibrating the ester solution and the base solution, followed by mixing into a flask under a nitrogen atmosphere, which was contained in a thermostated bath. Aliquots were periodically removed, quenched with a given volume of standardized hydrochloric acid solution, and then titrated with standardized sodium hydroxide solution to a phenolphthalein end point. The rates of basic hydrolysis of the peroxy-substituted esters **1b** and **5** were determined by glc analysis. The reaction procedure and quenching were the same as used in the titrimetric measurements. For the rate of appearance of *tert*-butyl alcohol, *n*-butyl alcohol was added to the stock ester solution as an internal standard. Anisole was added to stock solutions of **1b** and **5** as an internal standard to follow the rate of disappearance of the esters. The glc analysis of *tert*-butyl alcohol was performed on a 5 ft × 0.125 in. Porapak N (Waters Associates, Inc.) column at 120° with a nitrogen flow rate of 28 ml/min. Glc analyses for **1b** and **5** were carried out on a 5 ft × 0.125 in. 3% SE-30 on Varaport column at 60° with a nitrogen flow rate of 28 ml/min. A quantitative yield of *tert*-butyl alcohol was observed from the basic decomposition of **1b** by glc analysis with reference to an authentic mixture of *tert*-butyl alcohol and *n*-butyl alcohol. The glc data were processed by a first-order least squares program, where the input was time and relative areas of *tert*-butyl alcohol/*n*-butyl alcohol or ester/anisole. The kinetic data was usually gathered over 3 half-lives in both the glc and titrimetric measurements.

**Light Emission.**—A Hamamatsu R374 heat-on photomultiplier tube (PMT) supplied with 900 V was used to detect light emission *via* a Keithley 610A electrometer. The PMT was mounted at one window of a Bausch and Lomb 250-mm grating monochromator and a thermostated silicon oil bath was mounted at the other window. The thermostated compartment was machined from brass and contained a thermistor for temperature

(20) All melting points are corrected and boiling points are uncorrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to the internal tetramethylsilane standard as 0 ppm (δ scale). The nmr absorptions are given as parts per million, coupling, relative area. Infrared (ir) spectra were determined with a Perkin-Elmer 621 or 337 spectrometer and mass spectra were obtained with a Hitachi RMU-6E instrument. Glc analyses were performed on a Varian Aerograph Hy-Fi III (FID) instrument. Elemental analyses were performed by C. F. Geiger, Ontario, Calif.

(21) L. F. Feiser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1941, p 359.

(22) W. H. Richardson and R. S. Smith, *J. Org. Chem.*, **33**, 3882 (1968).

control, a heating element, a stirrer, a thermometer, a 1-cm cell mount, and quartz windows for absorption or fluorescence measurements. These windows could be capped on the exterior of the compartment so that chemiluminescence measurements could be made. The compartment was used in this mode for the light emission measurements and the monochromator was set at the "zero-order" position so that all wavelengths of light were detected. A basic 60% aqueous methanol solution, containing fluorescein, was placed in a 1-cm quartz cell, which was contained in the thermostated bath at 29°. The peroxide was then introduced into the solution with a 250-μl Hamilton syringe and the solution was mixed. The final sodium hydroxide and fluorescein concentrations were 0.50 and 0.008 $M$, respectively. The initial chloro-*tert*-butyl hydroperoxide and **1b** concentrations were $2.0 \times 10^{-2}$ and $4.0 \times 10^{-2} M$, respectively. Light emission increased to a maximum of 0.53 na and then began to decrease in the former solution. With **1b**, no light was detected within experimental error (±0.02 na).

**Registry No.**—**1a**, 16424-69-4; **1b**, 27492-18-8; **2a**, 35889-98-6; **2b**, 35889-99-7; **3a**, 35890-00-7; **3b**, 35890-01-8; **5**, 35890-02-9.

**Acknowledgment.**—We thank the U. S. Army Research Office (Durham) and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank William Koskinen and Mary Yelvington for the light-emission studies, and Dr. M. McElroy for an informative discussion of luciferin-AMP chemiluminescence.

# Base-Induced Rearrangement of Epoxides. V. Phenyl-Substituted Epoxides[1]

RANDOLPH P. THUMMEL AND BRUCE RICKBORN*

*Department of Chemistry, University of California, Santa Barbara, California 93106*

*Received June 8, 1972*

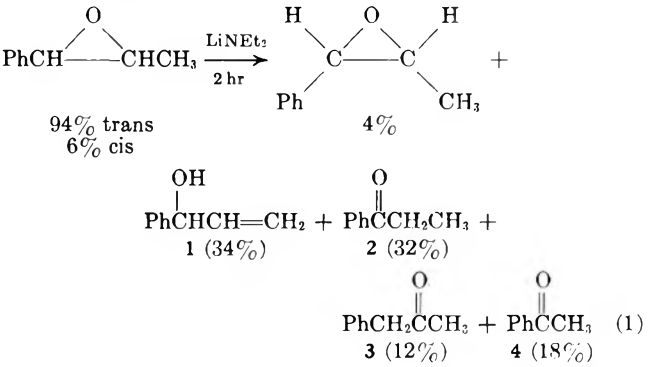
A number of α- and β-phenyl substituted epoxides have been subjected to lithium diethylamide treatment. The trans and cis isomers of β-methylstyrene oxide give different product distributions, but in both cases the β-elimination pathway is preferred over α-proton abstraction. The trans isomer leads to the formation of some acetophenone. Indene oxide gives a low yield of 1-indanone as the only isolable product. β-Phenyl substitution strongly affects the course of the epoxide to allylic alcohol rearrangement. For the first time in these reactions, some cis olefinic product is observed, formed preferentially from the trans isomer of 1-phenyl-2-butene oxide. The reactions of *trans*- and *cis*-3-phenylcyclohexene oxide substantiate a syn elimination mechanism.

Earlier work has established the strongly regioselective abstraction from the least substituted carbon in various alkyl-substituted epoxides,[2,3] the highly stereospecific formation of trans olefin[2,4] in these systems, and also the preferred syn elimination mechanism[5,6] in the reaction with lithium diethylamide. We have subsequently examined the base-induced reactions of various epoxides bearing substituents other than simple alkyl groups. This paper describes the results obtained with a number of α- and β-phenyl-substituted epoxides.

Cope and his coworkers[7] examined the reaction of some diarylethylene oxides with lithium diethylamide, and discovered some interesting stereochemical features. For example, *cis*-stilbene oxide gave 70% of deoxybenzoin, while *trans*-stilbene oxide gave 66% of diphenylacetaldehyde, both reactions occurring with high specificity. These illustrate the α-proton abstraction reaction pathway, various aspects of which have subsequently been explored in detail by Crandall, *et al.*[8]

## Results and Discussion

Epoxidation of commercial β-methylstyrene gave a distilled epoxide mixture which contained 94% trans and 6% cis isomer. This material was treated with a twofold molar excess of lithium diethylamide in refluxing ether–hexane for 2 hr to give the product mixture shown in eq 1.




(1)

Several interesting conclusions can be drawn from these data. First, the recovered epoxide proved to be essentially pure cis material (by vpc and ir), suggesting a considerable difference in rates of reaction for the isomeric epoxides;[9] this was substantiated by examining the reaction of isolated cis material, as discussed below. Second, examination of points taken during the course of eq 1 established that the allylic alcohol **1** was being converted fairly rapidly to the ketone **2** under the reaction conditions. In fact, extrapolation of these data suggests that no **2** is formed directly by an α-proton abstraction mechanism, but rather is generated exclusively by rearrangement of **1**. Similar allylic alcohol to ketone base-induced rearrangements have been previously observed[2,3,10] with terminal methylene allylic alcohols, and in the present system a more rapid reaction is anticipated because of the benzylic proton in **1**.

(1) (a) This work was supported in part by a grant from the Petroleum Research Fund, administered by the American Chemical Society (5744-AC4). (b) Part IV: C. K. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 2060 (1972).

(2) B. Rickborn and R. P. Thummel, *ibid.*, **34**, 3583 (1969).

(3) J. K. Crandall and L. C. Lin, *ibid.*, **33**, 2375 (1968).

(4) A. C. Cope and J. K. Heeren, *J. Amer. Chem. Soc.*, **87**, 3125 (1965).

(5) R. P. Thummel and B. Rickborn, *ibid.*, **92**, 2064 (1970).

(6) R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **36**, 1365 (1971).

(7) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **80**, 2844 (1958).

(8) J. K. Crandall, L. C. Crawley, D. B. Banks, and L. C. Lin, *J. Org. Chem.*, **36**, 510 (1971).

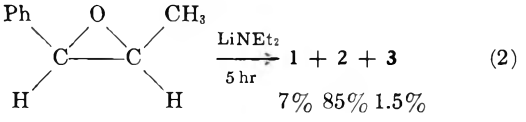
(9) This behavior stands in contrast to the reaction of *cis*- and *trans*-2-pentene oxide, where no significant difference in rates is observed.[2]

(10) C. K. Kissel and B. Rickborn, unpublished work.

Benzylmethyl ketone (**3**) is the only product clearly attributable to $\alpha$ abstraction; taking acidity into account suggests that the benzylic proton is attacked, followed by opening to a carbene and migration of the carbinol hydrogen to this center. This overall course of reaction must reflect the relative migratory aptitudes of hydrogen *vs.* methyl, since **3** arising by this mechanism from *trans*-$\beta$-methylstyrene oxide does not follow the stereochemical course observed by Cope[7] with the stilbene oxides. The relative amount of **1** plus **2** compared to **3** demonstrates the preference for $\beta$ elimination as opposed to $\alpha$ abstraction.

The formation of acetophenone (**4**) was unexpected, and no obvious analogy for the production of this material exists in the literature. Analysis of the early points taken in the reaction support the view that **4** is formed as a primary product from *trans*-$\beta$-methylstyrene oxide. Further work is underway to determine the mechanism of this reaction.

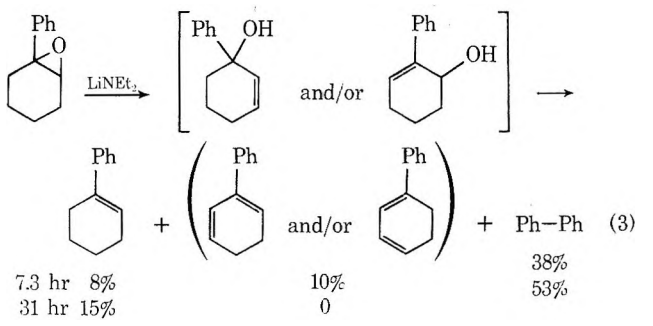
A sample of *cis*-$\beta$-methylstyrene oxide was obtained *via* epoxidation of predominantly cis olefin obtained by the Wittig reaction between ethylidenetriphenylphosphorane and benzaldehyde, and subsequent preparative vpc isolation. As anticipated from the results given in eq 1, the cis isomer was less reactive than the trans, 5 hr being required for >95% consumption of the epoxide. The results are given in eq 2.



(2)

The larger percentage of **2** relative to **1** is a reflection of the longer reaction time required in this reaction, and further substantiates the view that **2** is formed by a second-step rearrangement of **1** under the basic reaction conditions. An intriguing point is that the $\alpha$-abstraction process leading to **3** appears to be even slower with the cis than the trans epoxide; one might have expected the opposite result assuming that the methyl group in the trans isomer could sterically impede attack of the $\alpha$-benzylic hydrogen. No acetophenone was observed in the reaction of the cis epoxide.

The reaction of 1-phenylcyclohexene oxide with lithium diethylamide was briefly explored. This system illustrates another secondary process that is facilitated by the phenyl substituent, namely further elimination and disproportionation. The presumed allylic alcohol intermediates, shown in eq 3, were not isolated but are inferred from subsequent products.[11]

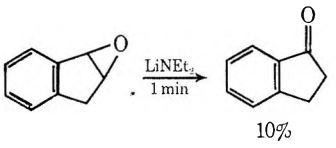


(3)

(11) Although not necessarily a good model for comparison with 1-phenylcyclohexene oxide, we have found that 1-*tert*-butylcyclohexene oxide undergoes a very slow reaction (47 hr) to give 95% of 1-*tert*-butyl-2-cyclohexenol and 5% of 2-*tert*-butyl-2-cyclohexenol.

A phenyl-substituted 1,3-cyclohexadiene is observed early in the reaction but disappears with time, presumably *via* disproportionation and by loss of LiH, forming 1-phenylcyclohexene and biphenyl by the first process, and biphenyl alone by the second. Literature precedents exist for both mechanisms under somewhat different reaction conditions,[12,13] as well a for the loss of $Li_2O$ to form the diene intermediate.[3]

Indene oxide undergoes very rapid reaction with lithium diethylamide, but yields only 10% of 1-indanone product, the remainder being resinous intractable material (eq 4). This system is of interest because

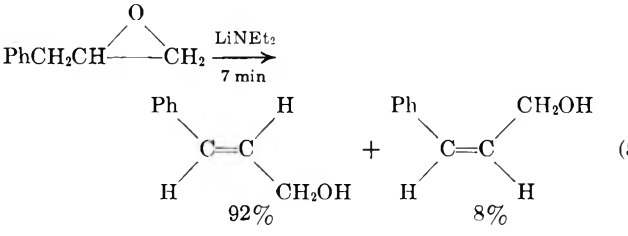


(4)

it has in effect both $\alpha$- and $\beta$-phenyl substitution, but also the geometry of a cyclopentene oxide, which appears not to be ideal for the $\beta$-elimination process.[14] Although this has not been established, we suggest that the 1-indanone arises by $\beta$ elimination followed by rearrangement of the allylic alcoholate. The intractable residue which accounts for most of the material could have arisen from the very reactive 2-indanone (a possible $\alpha$-abstraction product), but no evidence for this material was obtained.

A number of interesting observations were made in the base-induced rearrangements of $\beta$-phenyl-substituted epoxides.

The major product obtained on treating a terminal methylene oxide with lithium diethylamide is usually[15] the amino alcohol adduct formed by nucleophilic attack at the primary center. It was of interest to determine whether the acidifying effect of a $\beta$-phenyl substituent could overcome this alternative reaction, and to this end 3-phenyl-1-propene oxide was treated with lithium diethylamide. Two products were formed in a very fast, high-yield reaction, as shown in eq 5. The



(5)

acidifying effect of the phenyl substituent is clearly evident; not only is nucleophilic attack completely suppressed, but the rate of the $\beta$-elimination reaction is much greater than with a simple alkyl-substituted epoxide (under the same reaction conditions, abstraction from a secondary carbon in an open-chain epoxide requires several hours). The minor product of eq 5, *cis*-cinnamyl alcohol, is of interest since it represents

(12) J. E. Hofmann, P. A. Argabright, and A. Schriesheim, *Tetrahedron Lett.*, 1005 (1964).

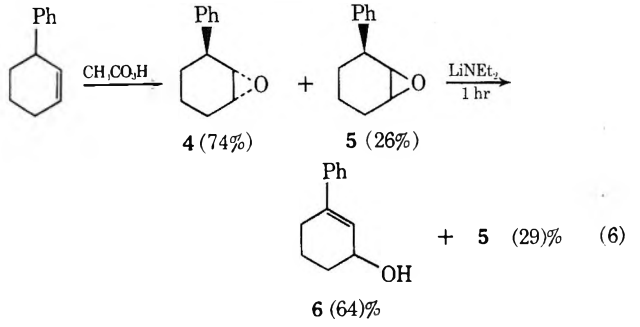
(13) R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *ibid.*, 199 (1967).

(14) J. K. Crandall and L. Chang, *J. Org. Chem.*, **32**, 435 (1967); these authors have reported that cyclopentene oxide on reaction with lithium diethylamide gives mostly amino alcohol adduct. A greater degree of elimination is obtained when a bulkier base (diisopropylamide) is employed.

(15) The course of these reactions is strongly dependent on other structural features of the substrate epoxide, the dialkylamide, and reaction conditions employed.[10]

the first example of any detectable cis olefin formed in a base-induced acyclic olefin oxide rearrangement. Both *cis*- and *trans*-cinnamyl alcohol are stable under the reaction conditions; so the distribution given in eq 5 represents a kinetically determined mixture rather than subsequent isomerization.

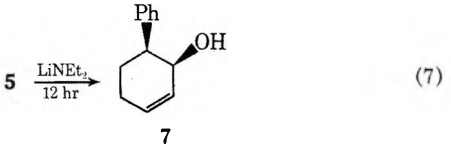
The formation of some cis olefin and the greatly enhanced rate of reaction associated with β-phenyl substitution raises the question of a possible difference in mechanism in these systems as compared to simple aliphatic epoxides. As noted earlier, the accumulated evidence dealing with alkyl-substituted epoxides all supports a syn elimination mechanism. In order to explore this question, 3-phenylcyclohexene was epoxidized and the resultant mixture of isomers was subjected to lithium diethylamide treatment (eq 6).




(6)

The results of the short-time treatment with base show clearly that the *trans*-3-phenylcyclohexene oxide reacts considerably faster than the cis isomer [the product distribution given in eq 6 does not show the small amount of biphenyl and related materials (4%) formed (see eq 3) nor the minor (3%) allylic alcohol derived from the cis epoxide (see below)]. Note that the formation of allylic alcohol **6** involves the abstraction of a tertiary benzylic proton cis to the epoxygen; in the absence of the acidifying phenyl group, no tertiary proton abstraction is observed.[6]

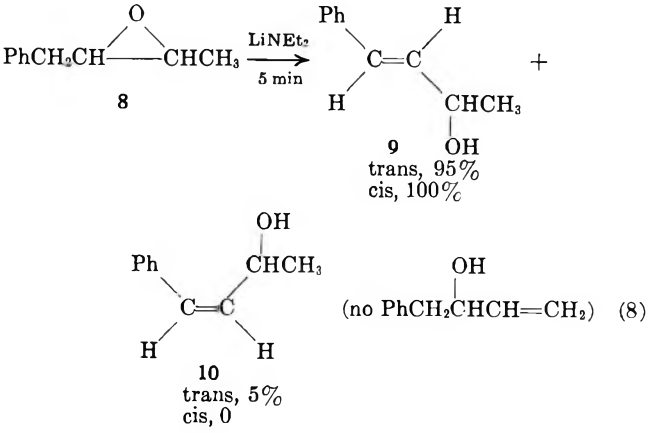
Distillation of the mixture obtained in eq 6 gave a sample of recovered epoxide which proved to be >98% pure cis material (**5**). This was in turn subjected to the basic reaction conditions, and in a much slower process gave **7**, derived from secondary proton abstraction, as the only allylic alcohol product (eq 7).




(7)

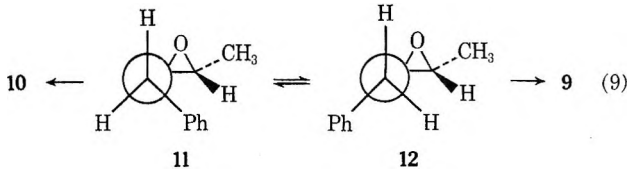
The results of eq 6 and 7 taken together strongly support the syn elimination mechanism, and demonstrate that, although the β-phenyl substituent exerts a significant acidifying effect, this is insufficient to overcome the geometrical requirements associated with the syn elimination process; *i.e.*, no anti elimination is observed with compound **5**.

Competition for abstraction between primary aliphatic and secondary benzylic protons leads to exclusive reaction by the latter pathway. This is illustrated by the reaction of 1-phenyl-2-butene oxide (**8**), eq 8, where no 1-phenyl-3-buten-2-ol is formed. Interestingly, the two isomers of this epoxide give somewhat




(8)

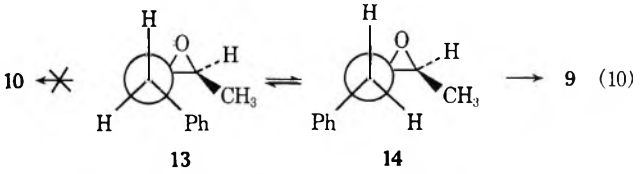
different product distributions; whereas the cis epoxide yields stereoisomerically pure trans olefin **9**, the trans epoxide, while giving 95% of the same product, also gives 5% of the cis allylic alcohol. The behavior of the trans epoxide in this respect resembles the reaction of 3-phenyl-1-propene oxide described earlier (eq 5). We can interpret these results in terms of a syn elimination mechanism as shown in eq 9 and 10. Consid-




(9)

ering first the trans epoxide, and viewing the Newman projections **11** and **12** as approximate models for the transition states for elimination, product **9** arises from conformer **12** in the favored process. Conformer **11** has an unfavorable 1,3-phenyl–hydrogen interaction (note that if phenyl is replaced by alkyl this process is excluded), leading to a smaller amount of cis olefin **10**.

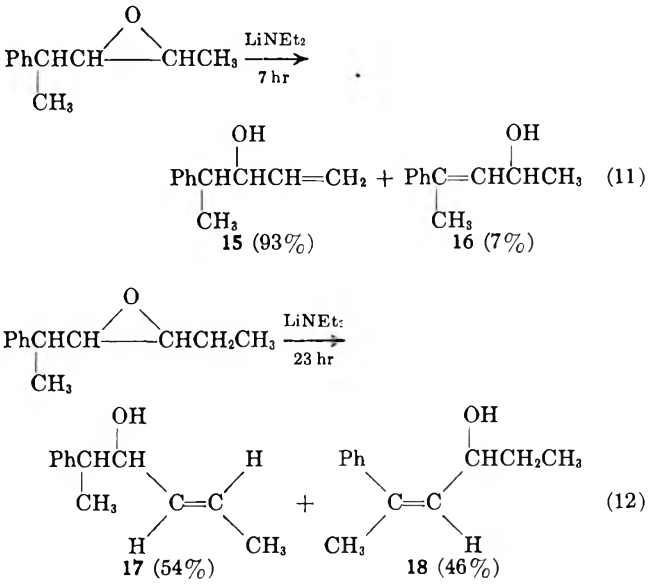
Similar depictions for the cis epoxide, shown in eq 10, point out the sterically unfavorable 1,3-phenyl–




(10)

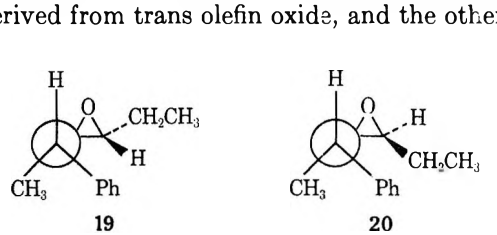
methyl interaction in conformer **13**; as a consequence of this steric effect in the transition state, all of the cis epoxide reacts *via* conformer **14** to give product **9**.

Finally, the question of competition between benzylic and aliphatic proton abstraction was explored in two systems, as shown in eq 11 and 12. Unfortunately, we do not know the exact stereochemistry of the starting epoxides in either case; both systems contain three asymmetric centers and therefore may involve mixtures of four diastereomerically related isomers (of course two of these centers are fixed relative to each other by the geometry of the starting olefin, but these proved to be very difficult to separate, and, even had we worked with single olefin isomers, the epoxide would have been a mixture of two diastereomers; see Experimental Section). Nonetheless, the results are of interest in that they clearly show that even tertiary ben-



zylic proton abstraction can compete with primary aliphatic proton abstraction.

The geometry of the minor product in eq 11 was not determined directly, but the gross structure was demonstrated by catalytic reduction to the saturated alcohol which in turn was compared with a sample produced by an alternate route. By analogy with the results of eq 8 and 12, it is presumed that the phenyl group of **16** is cis to the hydroxyalkyl function. Two allylic alcohols were formed, along with a number of minor products, in the reaction shown in eq 12; both were isolated by preparative vpc and appear to be homogeneous by spectral analysis. Compound **17** is presumed to have the trans geometry by analogy with earlier work.[4] The structure of **18** was deduced from its nmr spectrum, and in particular the geometry shown is based on the chemical shift ($\delta$ 5.32 ppm) of the vinyl proton, indicating that it lies outside the deshielding region of the aromatic ring and hence is trans to the phenyl group. Typically, when this proton is cis to the phenyl substituent, as in *trans*-cinnamyl alcohol, the resonance is observed at $\delta$ 6.2 ppm. Product **18** can arise by syn elimination from two diastereomers, one (**19**) derived from trans olefin oxide, and the other (**20**)



from cis olefin oxide. By analogy with eq 8, one would expect more facile reaction of **19** than of **20**; however, in view of the higher activation energy (longer reaction time) associated with the overall reaction in eq 12, formation of **18** from the cis olefin oxide **20** cannot be excluded on the basis of the present data. A substantial amount of epoxide (*ca.* 20%) is recovered even after the 23-hr time used in eq 12. It is likely that this material is diastereomerically enriched, but further efforts along these lines are hampered by the difficulty of separation of the epoxide diastereomers and the lack of a convenient method of assigning specific structures to these isomers.

## Experimental Section

All epoxidations were carried out with peracetic acid following a literature procedure,[16] at room temperature for periods of 12–20 hr.

The base-induced rearrangement yields, as determined by vpc using an internal standard and in several cases by distillation of products, were high (70–90%), except where otherwise noted. The products were stable to the vpc analytical conditions, as shown by isolation and reinjection. In the slower reaction systems, aliquots were analyzed at early stages of reaction, and product distributions were invariant except where otherwise noted. Individual geometric isomers of allylic alcohols resubjected to the basic reaction conditions are not interconverted.

***trans*-1-Phenyl-1-propene Oxide.**[17]—Commerical $\beta$-methylstyrene was epoxidized in 78% yield, giving material which was 6% cis and 94% trans (longer retention time on a Carbowax 20M vpc calumn) isomer.

Treatment of this mixture with lithium diethylamide in refluxing ether–hexane 2 gave a product showing five peaks by vpc at 155° (Carbowax 20M columns were used exclusively in this analysis and those described below); in order of retention time the first peak (8%) was not characterized, the second was unreacted cis epoxide (4%, ir identical with that of authentic sample), the third was acetophenone (by ir, nmr, and vpc, 16%), the fourth (41%) was a mixture, analyzed by nmr of the collected sample, of propiophenone (30%) and 1-phenyl-2-propanone (11%), and the fifth peak (31%) was 1-phenylallyl alcohol (**1**), identified by its characteristic nmr spectrum: $\delta$ 7.17 (s, 5 H), 6.15–5.6 (m, 1 H), 5.3–4.9 (m, 3 H, $CH_2$=CHCHOH), and 3.1 ppm (s, OH); ir 3350, 1495, 1027, 991, 764, and 703 $cm^{-1}$. The ratio of products changed with time as described in the text, as determined by analysis of aliquots taken during the course of the reaction.

***cis*-1-Phenyl-1-propene Oxide.**—The procedure of Schlosser and Christmann[18] was followed to give a mixture of olefins which was spinning band distilled to give a sample enriched in the cis isomer (62%). Epoxidation gave 69% of material, bp 53–55° (3.5 Torr), which showed two peaks (63:37) by vpc. The major peak (cis epoxide)[17] was isolated by preparative gas chromatography.

Lithium diethylamide rearrangement of this isomer gave after 5 hr a mixture analyzed as above: unreacted cis epoxide (*ca.* 1%), propiophenone (85%), and 1-phenyl-2-propanone (1.5%), unidentified (4.5%), and 1-phenylallyl alcohol (7%).

**1-Phenylcyclohexene Oxide.**[19,20]—Commercial 1-phenylcyclohexanol was dehydrated by heating with phosphoric acid in acetic acid solution. The 1-phenylcyclohexene,[21] bp 122–124° (12 Torr), gave on peracetic acid treatment 68% of the epoxide, bp 147–149° (26 Torr).

Treatment of the epoxide with lithium diethylamide for 7.3 hr resulted in a mixture showing six peaks by vpc analysis at 180°. The first three were in a ratio of 8:10:37 and were identified as 1-phenylcyclohexene (by spectral comparison with an authentic sample), 1- or 2-phenylcyclohexadiene, nmr $\delta$ 7.1 (m, 5 H), 6.3–5.7 (m, 3 H), and 2.2 ppm (m, 4 H), ir 3060–3010, 2920, 1590, 1074, 944, 820, 760, 730, 695, and 670 $cm^{-1}$, and biphenyl (by spectral comparison with commercial material). The remaining longer retention time products were not isolated or characterized. After 31 hr of lithium diethylamide treatment the phenylcyclohexadiene peak had disappeared and the first and third peaks were present in a ratio of 15:53.

**Indene Oxide.**—Epoxidation of indene gave 66% of the desired oxirane,[22] bp 88° (1.2 Torr), mp 29°; when subjected to lithium diethylamide, the epoxide was consumed within 6 min. The sole volatile product by vpc was 1-indanone (10%), identified by comparison with a published infrared spectrum.[23] The large amount of residue obtained on evaporation of solvent was

(16) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4329 (1960).

(17) R. C. Fahey and C. Schubert, *ibid.*, **87**, 5172 (1965).

(18) M. Schlosser and K. F. Christmann, *Angew. Chem.*, **76**, 683 (1964).

(19) The authors are indebted to John Widosh for carrying out the preparation of this material.

(20) S. Nametkin and N. Ivanoff, *Chem. Ber.*, **56**, 1805 (1923).

(21) R. Huisgen, F. Jakob, and R. Grashely, *ibid.*, **92**, 2206 (1959).

(22) W. Whitmore and A. Gebhart, *J. Amer. Chem. Soc.*, **64**, 912 (1942).

(23) R. Mecke and F. Langenbucher, "Infrared Spectra of Selected Chemical Compounds," Heyden, 1965, p 1061.

a viscous, intractable material which was not further characterized.

**3-Phenyl-1-propene Oxide.**—Epoxidation of allylbenzene gave 47% of product, bp 63–64° (4 Torr).[24] The reaction with lithium diethylamide was complete within a few minutes, leading in good yield to a mixture of two volatile products. The minor product (8%) was identified as *cis*-cinnamyl alcohol by its nmr spectrum: δ 7.1 (s, 5 H), 6.4 (d, 1 H, $J$ = 12 Hz, ArC**H**), 5.72 (d of t, 1 H, $J_{23}$ = 12 Hz, $J_{21}$ = 6 Hz, CH=C**H**CH$_2$OH), 4.25 (d of d, 2 H, $J$ = 6, 1.5 Hz, C**H**$_2$OH), and 2.9 ppm (s, OH); ir 3350, 1600, 1030, 777, and 703 cm$^{-1}$. The major product (92%) was *trans*-cinnamyl alcohol, identified by spectral comparison with commercial material.

**3-Phenylcyclohexene Oxide.**—NBS treatment of cyclohexene was used to prepare 3-bromocyclohexene. This was in turn added to phenylmagnesium bromide in ether at 0° to give 3-phenylcyclohexene[25] in 93% distilled yield, bp 77° (3 Torr). Epoxidation gave 85% of material, bp 106° (3 Torr), which showed two peaks (area ratio 74:26) on vpc analysis at 180°.

*Anal.* Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.36; H, 3.34.

The stereochemical identification of the major epoxide as trans and the minor as cis is based on evidence presented below.

Treatment of the epoxide mixture with lithium diethylamide for 55 min gave a product which exhibited six peaks on vpc analysis at 188°. The first three peaks (4% total) were presumed to be phenylcyclohexadienes and biphenyl (the latter by coinjection); the fourth peak (29%) was unreacted cis epoxide; the fifth peak (3%) corresponded to 6-phenyl-2-cyclohexenol, presumably derived from the cis epoxide (see below). The last peak (64%) was identified as 3-phenyl-2-cyclohexenol:[26] nmr δ 7.02 (m, 5 H), 5.9 (s, OH), 4.13 (broad s, C**H**OH), and 2.5–1.2 ppm (m, 6 H); ir 3325, 3070–3010, 1490, 1440, 1160, 1055, 977, 760, and 698 cm$^{-1}$. This material on reinjection into the vpc underwent partial dehydration to give the phenylcyclohexadienes (peaks 1 and 2). Catalytic hydrogenation on Pd/C gave a mixture of 58% *cis*- and 42% *trans*-3-phenylcyclohexanol.

***cis*-3-Phenylcyclohexene oxide** recovered from the above experiment was resubjected to lithium diethylamide treatment to give after 12 hr 6-phenyl-2-cyclohexenol[26] in high yield: nmr δ 7.0 (s, 5 H), 5.65 (m, 2 H), 3.7 (m, C**H**OH), 2.6 (m, ArC**H**), 1.9 (s, OH), 2.4–1.3 (m, 4 H); ir 3380, 3070–3010, 2910, 1605, 1072, 990, 940, 758, and 701 cm$^{-1}$.

Lithium aluminum hydride reduction of a sample of cis epoxide gave a mixture of 91% *cis*- and 9% *trans*-2-phenylcyclohexanol (the latter arising by the oxidative inversion mechanism[27]); these products were distinguishable by vpc from the 3-phenylcyclohexanols obtained above by catalytic hydrogenation.

***trans*-1-Phenyl-2-butene Oxide.**—Commercial 1-phenyl-2-butene (Aldrich, 96% trans) was epoxidized in 83% yield, bp 107–108° (7.5 Torr), and a sample of pure trans epoxide was isolated by preparative vpc: nmr δ 6.9 (s, 5 H), 2.37 (s over m, 4 H), and 0.8 ppm (d, 3 H, $J$ = 5 Hz); ir 3080–3020, 1610, 1500, 1460, 1390, 954, 858, 805, 743, and 704 cm$^{-1}$.

Reaction with lithium diethylamide was complete in 5 min, leading to two products in high yield. The major product (95%) was *trans*-4-phenyl-3-buten-2-ol:[28] nmr δ 7.08 (s, 5 H), 6.18 (m, 2 H), 5.0 (s, OH), 4.33 (d of q, C**H**OH), and 1.27 ppm (d, 3 H, $J$ = 6 Hz), agrees well with *trans*-cinnamyl alcohol; ir 3340, 3080–3020, 2970, 1145, 1060, 968, 944, 750, and 696 cm$^{-1}$.

The minor product (5%) had the shorter vpc retention time, and was identified as *cis*-4-phenyl-3-buten-2-ol[28] by its spectra: nmr δ 7.06 (s, 5 H), 6.26 (d, $J$ = 11 Hz, ArC**H**), 5.50 (d of d, $J$ = 11, 8 Hz, CH=C**H**CHOH), 4.58 (d of q, $J$ = 8, 6 Hz, C**H**OH), 2.48 (s, OH), and 1.22 ppm (d, 3 H, $J$ = 6 Hz); ir 3340, 3070–3010, 2960, 1110, 1053, 930, 915, 870, 795, 768, and 700 cm$^{-1}$.

When the reaction with lithium diethylamide was carried out for 22 hr a new product (64%) appeared at the expense of the trans allylic alcohol so that the product ratio became 64:6:30. The new product was identified as 4-phenyl-2-butanone: nmr δ 7.0 (s, 5 H), 3.68 (two t, 4 H), and 1.97 ppm (s, 3 H); ir 1715 cm$^{-1}$.

***cis*-1-Phenyl-2-butene Oxide.**—The procedure of Hauser, *et al.*,[29] was followed for the Wittig reaction of phenylacetaldehyde and ethylidenetriphenylphosphorane; 26% of olefin, bp 61–62° (11 Torr), was obtained, which by vpc analysis showed two poorly resolved peaks in a ratio of 25:75. The minor olefin was identical by coinjection with commercial trans material.

Epoxidation of this mixed olefin gave 66% of material which showed two peaks (ratio 79:21) on vpc analysis at 170°. The minor peak corresponded to *trans*-1-phenyl-2-butene oxide by coinjection. The major product (cis epoxide) was collected by preparative vpc.

The pure cis isomer again reacted very rapidly with lithium diethylamide to give a quantitative yield of *trans*-4-phenyl-3-buten-2-ol, analyzed as in the previous experiment. After 9-min reaction time, no other products could be detected.

**4-Phenyl-2-pentene Oxide.**—The procedure of Schlosser and Christmann[18] was followed, using 2-phenylpropionaldehyde and ethyltriphenylphosphonium bromide, to obtain 42% of 4-phenyl-2-pentene, bp 77.5–79° (20 Torr); attempts to separate the olefin isomers were unsuccessful. Epoxidation gave material, bp 82–84° (7 Torr), which showed only two peaks (9:91) on vpc analysis at 150°. Treatment of this epoxide mixture with lithium diethylamide for 6.6 hr gave two products in overall high yield. The major product (93%) was collected and identified as 4-phenyl-1-penten-3-ol by its characteristic nmr: δ 7.02 (s, 5 H), 5.9–4.8 (ABC pattern, 3 H, CH=C**H**$_2$), 4.0 (t, $J$ = 5.5 Hz, C**H**OH), 2.73 (quintet, $J$ = 7 Hz, ArC**H**), 2.13 (s, OH), and 1.25 ppm (d, 3 H, $J$ = 7 Hz); ir 3400, 3070–3015, 2960, 1599, 1495, 1450, 1130, 995, 924, 764, and 703 cm$^{-1}$.

The minor product could not be isolated but was presumed to be 4-phenyl-3-penten-2-ol by catalytic hydrogenation of the product mixture and comparison with the products of lithium aluminum hydride reduction of the starting epoxide.

**2-Phenyl-3-hexene Oxide.**—The olefin was prepared as in the previous experiment by the modified Wittig reaction of 2-phenylpropionaldehyde and *n*-propyltriphenylphosphonium bromide. A 69% yield of material, bp 63–73° (6 Torr), was obtained; no separation of the cis and trans isomers could be effected. Peracetic acid treatment gave a product which showed four peaks (8:63:10:19) by vpc at 120°. Careful spinning-band distillation gave a sample containing only the second and third components in a ratio of 86:14, bp 88° (4.5 Torr). The latter mixture was subjected to lithium diethylamide treatment for 23 hr, after which it was analyzed by vpc at 175°, giving nine peaks. The first six peaks were collected in pairs and the last three separately. The first two peaks (9 and 1%) appeared to be dienes by virtue of their volatility and ir spectrum; of the second pair, peak three (18%) was unreacted epoxide, and the fourth (2%) was not identified. The fifth and sixth peaks (4 and 1%) were characterized only by ir: 3070–3020, 2960, 1495, 1450, 1380, 1200, 1170, 1068, 760, and 700 cm$^{-1}$. The seventh peak (27%) was *trans*-5-phenyl-4-hexen-3-ol: nmr δ 7.06 (s, 5 H), 5.32 (d, $J$ = 9 Hz, C=CH), 3.85 (d of t, $J$ = 9.6 Hz, CHOH), 3.2 (s, OH), 1.95 (s, 3 H, C=CCH$_3$), 1.38 (q, 2 H, $J$ = 7 Hz), and 0.85 ppm (t, 3 H, $J$ = 7 Hz); ir 3330, 3070–3015, 2960, 2930, 1495, 1445, 1075, 1030, 997, 961, 771, and 705 cm$^{-1}$. The eighth peak (33%) was identified as *trans*-2-phenyl-4-hexen-3-ol by its nmr: δ 7.0 (s, 5 H), 5.32 (m, 2 H), 3.96 (t, $J$ = 5.5 Hz, CHOH), 2.7 (quintet, $J$ = 6.5 Hz, ArCH), 2.1 (s, OH), 1.6 (d, 3 H, $J$ = 4.5 Hz), and 1.25 ppm (d, 3 H, $J$ = 6.5 Hz); ir 3375, 3080–3020, 2960, 1495, 1455, 1380, 1010, 968, 760, 705 cm$^{-1}$. The final vpc peak (5%) was an amino alcohol adduct, based on its mass spectrum: $m/e$ 71, 91, 105, 249 (parent). The first six peaks, with the exception of the unreacted epoxide, all appear to be secondary reaction products or formed by minor decomposition of the allylic alcohols on vpc injection.

**Registry No.**—**1**, 4393-06-0; *trans*-**4**, 36004-00-9; *cis*-**5**, 36004-01-0; *trans*-**8**, 32215-84-2; *cis*-**8**, 36004-03-2; **9**, 36004-04-3; **10**, 31915-95-4; **15**, 36004-05-4; **17**, 36004-06-5; **18**, 36004-07-6; *trans*-1-phenyl-1-propene oxide, 23355-97-7; *cis*-1-phenyl-1-propene oxide, 4541-87-1; 1-phenylcyclohexene oxide, 4829-01-0; indene oxide, 768-22-9; 3-phenyl-1-propene oxide, 4436-24-2; *cis*-cinnamyl alcohol, 4510-34-3; 4-phenyl-2-pentene oxide, 36004-14-5; 2-phenyl-3-hexene oxide, 36004-15-6.

(24) N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J. Chem. Soc.*, 1925 (1959).

(25) A. Berlande, *C. R. Acad. Sci.*, **213**, 437 (1941).

(26) A. Mandrou, P. Potin, and R. Wylde-Lachazette, *Bull. Soc. Chim. Fr.*, 1546 (1962).

(27) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964).

(28) Y. Pocker and M. J. Hill, *J. Amer. Chem. Soc.*, **93**, 691 (1971).

(29) C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).

# INDO Molecular Orbital Study of α-Heteroatom Nitrenes

LARRY J. HAYES,*[1a] FRANK P. BILLINGSLEY, II, AND CARL TRINDLE

*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901*

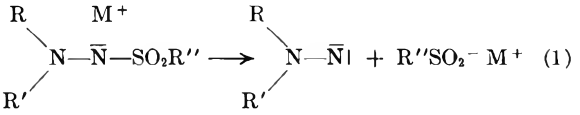
*Received February 17, 1972*

The results of INDO valence-shell electron molecular orbital calculations are reported for a number of heteroatom (O, N, S) substituted nitrenes to provide a framework in which to evaluate the experimental observations on these intermediates. Geometry searches have been performed for the simplest species, HON, and $H_2NN$, indicating that both molecules are bound in preferred singlet ground states. Computed atomic charges and binding energies are shown to be consistent with the observed relative reactivities of the various nitrenes toward electrophilic olefins.

The chemistry of diazenes[1b,2] (*i.e.*, the 1,1-disubstituted species, **1**) and oxynitrenes,[3] **2**, have been of

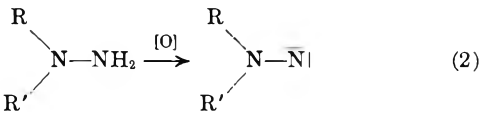
**1** **2**

considerable recent interest. Diazenes have been generated by thermal decomposition of 1,1-disubstituted 2-sulfoxyhydrazine salts (eq 1) and by oxidation



(1)

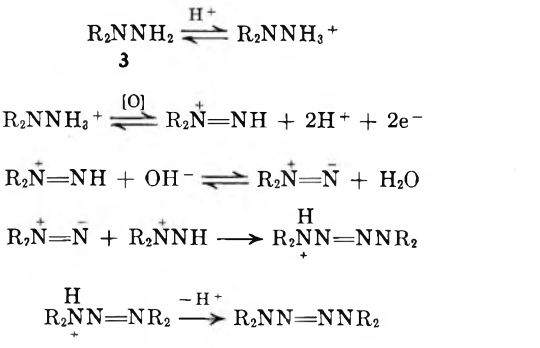
of a variety of *N*-amino compounds (eq 2).



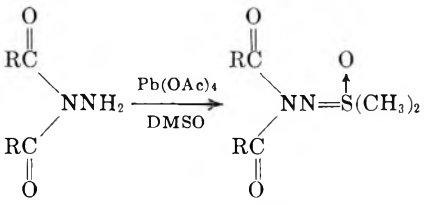
(2)

McBride[4] has elegantly shown that the oxidation of 1,1-dialkylhydrazines, **3**, in acidic solution proceeds *via* a diazene (Scheme I).

SCHEME I



Diazenes generated by oxidation reactions have been trapped in several cases.[5-8] When acyl-substituted hydrazines were oxidized with lead tetraacetate in dimethyl sulfoxide, the diazene was trapped by dimethyl sulfoxide to give dimethylsulfoximine derivatives[6] (eq 3). The diazene has been regenerated by

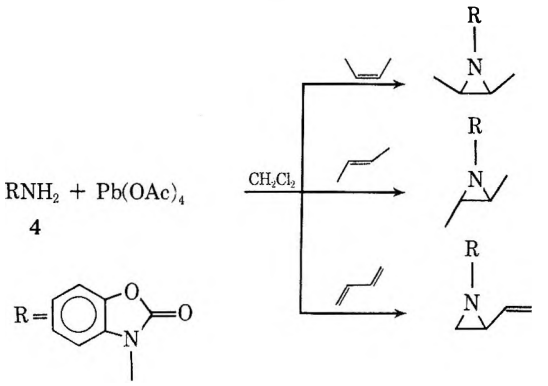


(3)

thermolysis and photolysis of the sulfoximines to give identical products as are obtained from oxidation of the corresponding hydrazine in the absence of dimethyl sulfoxide.

Lead tetraacetate oxidation of 3-aminobenzoxazolineone (**4**) in the presence of olefins and dienes yielded the corresponding aziridine[7] (Scheme II). The stereo-

SCHEME II



specific additions to cis and trans olefins and the 1,2 addition to 1,3-butadiene all indicate a singlet diazene intermediate. This is further substantiated by stereospecific addition, even at low olefin concentration.

Recently, Rees and coworkers[8] have found that electrophilic olefins, those substituted with inductively or conjugatively electron-withdrawing groups, were effective "traps," and in some cases gave a higher yield of the aziridine. This fact, along with the singlet character of the nitrene, was explained by delocaliza-

(1) (a) Correspondence to this author should be mailed to Air Products and Chemicals, Inc., P. O. Box 538, Allentown, Pa. 18105. (b) For a review see W. I. Lwowski, Ed., "Nitrenes," Interscience, New York, N. Y., 1970, Chapter 10.

(2) (a) C. G. Overberger, M. Valentine, and J. P. Anselme, *J. Amer. Chem. Soc.*, **91**, 687 (1969), and references cited therein; (b) D. M. Lemal, T. W. Rave, and S. D. McGregor, *ibid.*, **85**, 1944 (1963).

(3) J. H. Boyer and J. D. Woodyard, *J. Org. Chem.*, **33**, 3329 (1968); A. Hassner, R. Wiederkehr, and A. J. Kascheres, *ibid.*, **35**, 1962 (1970).

(4) (a) W. R. McBride and H. W. Kruse, *J. Amer. Chem. Soc.*, **79**, 572 (1957); (b) W. H. Urry, H. W. Kruse, and W. R. McBride, *ibid.*, **79**, 6568 (1957); (c) W. R. McBride and E. M. Bens, *ibid.*, **81**, 5546 (1959).

(5) Reference 1, p 361.

(6) D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *Chem. Commun.*, 146 (1969); C. W. Rees and M. Yelland, *ibid.*, 377 (1969).

(7) R. S. Atkinson and C. W. Rees, *ibid.*, 1230 (1967); R. S. Atkinson and C. W. Rees, *J. Chem. Soc. C*, 772 (1969).

(8) D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *ibid.*, 576 (1970).

tion of the lone pair of the tervalent nitrogen into the vacant p orbital of the univalent nitrogen. This could

$$R_2NN \longrightarrow R_2\overset{+}{N}{=}\overset{-}{N}$$

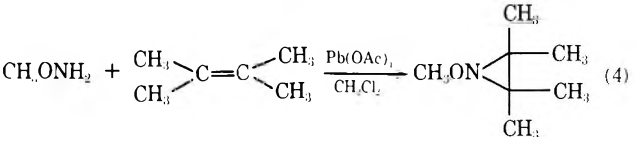
cause the singlet to be the ground state and would also increase the nucleophilic character of the intermediate.

Lemal[9,10] has shown that diazenes are generated by α elimination of 1,1-dialkyl-2-arenesulfonylhydrazines on treatment with base to yield tetrazenes. However, there have been no reports of addition of the dialkyl-

$$R_2NNHSO_2Ph \xrightarrow{\text{base}} R_2NN{=}NNR_2$$

diazene generated by base treatment to olefins or dialkyldiazene insertion into C–H bonds.

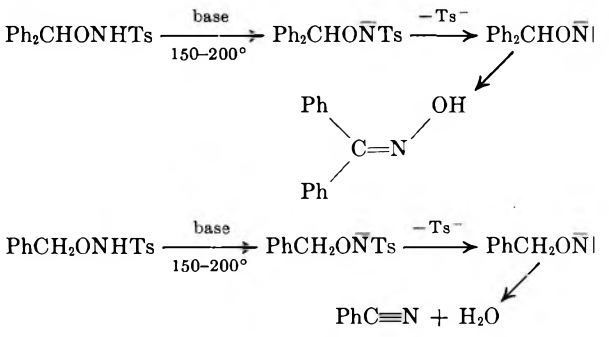
An oxynitrene has been postulated as an intermediate in the lead tetraacetate oxidation of methoxyamine in the presence of tetramethylethylene[11] (eq 4).



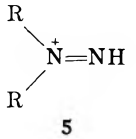
(4)

When *O*-benzhydryl-*N*-*p*-toluenesulfonylhydroxylamine or *O*-benzyl-*N*-*p*-toluenesulfonylhydroxylamine were treated with base (sodium hydride or butyllithium) in triglyme and heated at 150–200°, O to N migration occurred.[12] An oxynitrene intermediate could explain the results (Scheme III).

Scheme III



Lemal and coworkers[10] have shown that diazenium ions, **5**, can be generated at room temperature. However, we have found that oxynitrenium cations, **6**, were



**5**

**6**

not formed even with prolonged heating at 56° under the same reaction conditions.[13]

Since heteroatoms adjacent to a nitrene are believed to stabilize the nitrene, a comparison of the stabilizing effects of some heteroatoms was done. Reported here are the results of LCAO–MO–SCF calculations on a number of heteroatom (O, N, S) substituted nitrenes which provide a more systematic framework on which to base conclusions from experimental observations.

**Method.**—Approximate LCAO–MO calculations for those systems containing only first-row atoms were performed using the INDO (intermediate neglect of differential overlap) method.[14,15] This semiempirical model employs a minimum basis set of valence shell atomic orbitals (AO's) and neglects differential overlap in all two-electron integrals except one-center exchange types. For HSN, the CNDO (complete neglect of differential overlap) method, as modified for second-row elements, was employed.[16,17] Both the INDO and CNDO methods are documented to be quite successful in reproducing various molecular properties: experimental bond angles are predicted with good accuracy; calculated bond distances are less satisfactory, but still exhibit good correlation with observed values; dipole moments normally agree remarkably with the experimental quantities; and calculated binding energies are typically high in magnitude. Computations were carried out with the standard CNINDO program[18] on a Burroughs B5500 computer.

To obtain a qualitative estimate of bonding from our calculations, we computed a bond index,[19-21] $W_{ab}$, which is simply the square of the bond order, where

$$W_{ab} = (P_{ab})^2 = \sum_{i}^{occ} \sum_{j}^{MO's} c_{ia}c_{ib}c_{ja}c_{jb} \qquad (5)$$

i and j label the doubly occupied MO's and a and b label AO's in the LCAO expansion. The total bond index between two atoms, $W_{AB}$, is then obtained by summing $W_{ab}$ over all AO's on atoms A and B.

$$W_{AB} = \sum_{a}^{on\ A} \sum_{b}^{on\ B} W_{ab} \qquad (6)$$

Molecular geometries for HON, $H_2NN$, and HSN were obtained by minimizing the total energy of each system with respect to all bond angles (except for the out-of-plane angle for $H_2NN$) and bond distances. Bond lengths for LiON were taken from Andrews' infrared study[22] followed by minimization of the total energy with respect to the LiON bond angle. $CH_3ON$ was constructed by replacing the hydrogen in HON with a methyl group at the computed equilibrium configuration. Finally, the geometry of succinimidonitrene was based on the X-ray structure of succinimide.[23]

The relative stabilities of nitrenes is a question of considerable interest, and cannot be answered simply by quoting the total binding energies estimated in the available INDO programs. Total binding energies would lead one to the conclusion that large systems are

(9) D. M. Lemal, F. Menger, and E. Coats, *J. Amer. Chem. Soc.*, **86**, 2395 (1964).

(10) D. M. Lemal, C. D. Underbrink, and T. W. Rave, *Tetrahedron Lett.*, 1955 (1964).

(11) S. J. Brois, *J. Amer. Chem. Soc.*, **92**, 1079 (1970).

(12) F. A. Carey and L. J. Hayes, *J. Amer. Chem. Soc.*, **92**, 7613 (1970).

(13) F. A. Carey and L. J. Hayes, 1971, unpublished data.

(14) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967).

(15) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970, Chapters 3 and 4 and references to other works cited therein.

(16) D. P. Santry and G. A. Segal, *J. Chem. Phys.*, **47**, 158 (1967).

(17) D. P. Santry, *J. Amer. Chem. Soc.*, **90**, 3309 (1968).

(18) P. A. Dobosh, Program No. 141 of the Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind.

(19) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

(20) C. Trindle and O. Sinsnoglu, *J. Amer. Chem. Soc.*, **91**, 853 (1969).

(21) C. Trindle, *ibid.*, **91**, 219 (1969).

(22) L. Andrews, 1971, personal communication.

(23) R. Mason, *Acta Crystallogr.*, **9**, 405 (1956).

inevitably more stable than small systems; however, this implication is a direct consequence of the obvious fact that larger molecules have more bonds and hence more binding energy than small molecules.

Hess and Schaad[24] show us how to deal properly with binding energies, by analogy with their treatment of Hückel delocalization energies. Recognizing that acyclic polyenes have little $\pi$ delocalization, Hess and Schaad represented the $\pi$ energy of these systems as a superposition of "bond" contributions. The resonance stabilization for cyclic systems is the residual $\pi$ energy after bond contributions are set aside. This approach clarified a number of paradoxes associated with the customary predictions of stability based on Hückel energies.

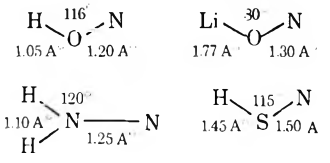
We collected INDO binding energies for 18 molecules containing the kinds of bonds typically encountered in organic systems of H, C, N, and O. This number is smaller than we had wished, because we limited our attention to molecules for which energy-optimized geometries had been determined.[25] Experience shows that optimized geometries are essential to meaningful estimates of features of potential surfaces.[26] All these molecules can be represented by a single dominant valence bond structure, and should, therefore, have highly localizable charge distributions. Multiple regression analysis[27] enabled us to generate a number of binding energy predictor equations, of linear form in the number of bonds of distinct types.

The best *single* predictor of binding energy is the total number of bonds, irrespective of type. This reflects the fact that binding energy must increase with the number of bonds, as anticipated. Almost 88% of the variance in binding energy is accounted for by the number of bonds. Total valence electrons is a less suitable measure, since lone pairs make little contributions to the binding energy. One may generate predictor formulas by considering only molecules without $\alpha$-nitrene fragments, or by including such molecules in the sample. The proper choice is not clear; so we made both in turn.

## Results

Geometry searches were carried out for HON, LiON, $H_2NN$, and HSN. All four molecules were found to be bound, and in Chart I, the equilibrium geometries

CHART I
COMPUTED EQUILIBRIUM GEOMETRIES




at the potential minima are presented. LiON has been isolated by Andrews in an argon matrix, and our calculated bond angle of 80° agrees well with the experimentally estimated value (77.7°).[22] To our knowledge, HON, $H_2NN$, and HSN have not yet been isolated; however, HON and $H_2NN$ are the simplest homologs of the intermediates which have been postulated in certain reactions.

Listed in Table I are the computed total energies and binding energies for all of the nitrenes considered in this work. For HON, $CH_3ON$, and $H_2NN$ we computed both the singlet and triplet (using optimum singlet geometries) species. In all three cases, the singlet species is predicted to be more stable than the triplet, generally by more than 1 au.

TABLE I
COMPUTED TOTAL AND BINDING ENERGIES

| Registry no. | Molecule | Multiplicity | Total energy, au | Binding energy, au |
|---|---|---|---|---|
| 35337-59-8 | HON | Singlet | −29.2925 | −0.6885 |
| | HON | Triplet | −28.0893 | 0.5147 |
| 35337-60-1 | $CH_3ON$ | Singlet | −37.6439 | −1.8276 |
| | $CH_3ON$ | Triplet | −36.0014 | −0.1850 |
| 36529-65-4 | LiON | Singlet | −28.7600 | −0.5625 |
| 35337-54-3 | $H_2NN$ | Singlet | −23.6459 | −1.0221 |
| | $H_2NN$ | Triplet | −22.5992 | 0.0246 |
| 36529-67-6 | HSN[a] | Singlet | −22.6646 | −0.1832 |
| | HSN[b] | Singlet | −22.8056 | −0.3241 |
| 36529-68-7 | Succinimidonitrene | Singlet | −87.6437 | −5.4184 |

[a] CNDO without d orbitals on sulfur. [b] CNDO with d orbitals on sulfur.

The relative stabilities of these nitrenes can be predicted by using linear predictor formulas. It was found that, if nitrenes are excluded, linear predictor formulas contain a root-mean-square error of *ca.* 0.1 au, or 4–10%. Departures of computed INDO binding energies from binding energies estimated from the predictor formulas must exceed 0.2 au if we are to attach any significance to the disparity. Of the $\alpha$-heteronitrenes LiON falls below the predicted binding energy, $CH_3ON$, $H_2NN$, and HON are accurately predicted, while succinimidonitrene is exceedingly stabilized relative to the estimate of the predictor. The order of stability of $\alpha$-heteroatom nitrenes is indicated to be succinimidonitrene $\gg$ $CH_3ON$ > $H_2NN$ > LiON $\sim$ HON.

If one includes nitrenes in the sample of data from which the predictor equation is constructed, the quality of the linear predictions diminishes; there is more scatter in the data, due in part to the fact that nitrenes are not so highly localized as more common bonds. The best predictor equation makes reference to total bonds, CO double bonds, and CC double bonds. It accounts for 98% of variance in our data, with a residual error (root mean square) of 0.13 au. Inspection of predicted binding energies and INDO computed values shows that succinimidonitrene's stability is high, LiON's is low, and the other stabilities are unsurprising. This trend agrees in large part with the trends observed above, *even though the nitrene binding energies are now influencing the predictor equation.*

The calculated net atomic charges are displayed in Chart II. It is significant to note the existence of a substantial charge separation within each molecule and a relatively large negative charge on each of the

(24) R. A. Hees, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **93**, 305 (1971); see also M. J. S. Dewar and C. de Llano, *ibid.*, **91**, 789 (1969).

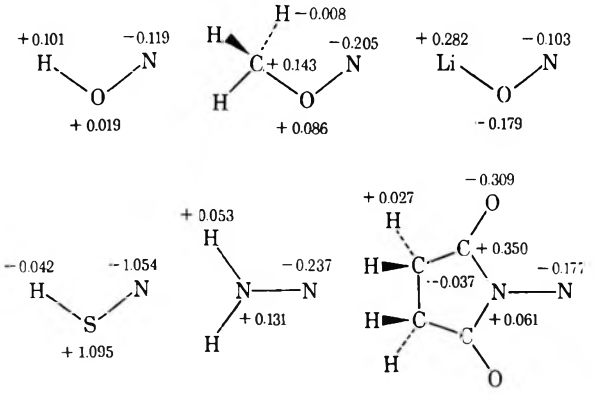
(25) M. S. Gordon and J. A. Pople, *J. Chem. Phys.*, **49**, 4643 (1968); see also ref 14; J. A. Pople, D. L. Beveridge, and N. S. Ostlund, *Int. J. Quantum Chem.*, **1**, 293 (1967).

(26) M. S. Gordan, *J. Amer. Chem. Soc.*, **91**, 3122 (1969).

(27) A particularly convenient vehicle for this analysis is the SPSS (Statistical Package for the Social Sciences) program described in N. Nie, D. H. Bent, and C. H. Hull, "SPSS," McGraw-Hill, New York, N. Y., 1970.

Chart II

Computed Net Atomic Charges




nitrene nitrogens. The variation of this negative charge among the molecules correlates well with the expected nature of the nitrene substituents. On passing from HON to $CH_3ON$, the negative charge increases from −0.119 to −0.237, consistent with the electron-donating character of the methyl group. In comparing $H_2NN$ and succinimidonitrene, one would expect a substantial lowering of the negative charge in the latter due to the electron-withdrawing capabilities of the adjacent carbonyl groups. This hypothesis is borne out by the INDO calculations, but not to the extent that has been previously postulated for this molecule. For HSN, the CNDO calculation including d orbitals yields a net charge of −1.054 on the nitrene nitrogen. This figure is nearly five times greater than that for any of the other molecules. In comparing HON with $H_2NN$, we note that the oxygen in HON transfers less charge to the nitrene nitrogen than the corresponding nitrogen in $H_2NN$.

The computed dipole moments are tabulated in Table II, and are entirely consistent with the predicted

Table II

Computed Dipole Moments

| Molecule | Dipole moment, D |
|---|---|
| HON | 2.18 |
| $CH_3ON$ | 2.86 |
| LiON | 4.88 |
| $H_2NN$ | 3.19 |
| HSN[a] | 9.09 |
| Succinimidonitrene | 5.25 |

[a] CNDO with d orbital on sulfur.

large separation of charge in these molecules evidenced in Chart II. In view of the previous success of the INDO and CNDO methods in reproducing known molecular dipole moments, it is not unreasonable to postulate that the computed figures lie within one Debye of the true values.

Finally, in Table III, we present the total indices, $W_{AB}$, for the nitrene bond in each of the substituents. The electron-donating character of the methyl group has increased the ON bond index in $CH_3ON$ relative to HON, and the electron-withdrawing nature of the carbonyl groups in succinimidonitrene have decreased the NN bond index relative to $H_2NN$. All of the nitrene bond indices, except that for HSN, lie between one and two, implying partial double bond character for these bonds.

Table III

Computed Bond Indices

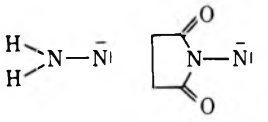
| Molecule | Bond index ($W_{XN}$) |
|---|---|
| HON | 1.69 |
| $CH_3ON$ | 1.74 |
| LiON | 1.69 |
| $H_2NN$ | 1.87 |
| HSN[a] | 2.54 |
| Succinimidonitrene | 1.44 |

[a] CNDO with d orbitals on sulfur.

## Discussion

The INDO calculations for the diazenes and oxynitrenes have given us a better understanding of the chemistry of these intermediates. In the geometry searches (by varying one parameter and keeping the remaining constant until a minimum was obtained), potential minima were found for both HON and $H_2NN$, indicating that both molecules should be bound. Replacement of the hydrogen in HON with a methyl group caused an increase in stability of the nitrene, which suggests that the alkylated nitrenes should be more stable than the unsubstituted compounds.

Diazenes are known to add to olefins stereospecifically,[7,8] which is in agreement with the calculated ground state singlet for isodiimide (7) and the predicted high stability of the singlet succinimidonitrene (8).




7 8

The nucleophilic character of diazenes toward electrophilic olefins[8,28] can be explained on the basis of the predicted negative charge localized on the nitrene nitrogen of these intermediates. The addition of the methyl group to HON caused a substantial increase in the negative charge on the nitrene nitrogen, which can qualitatively be interpreted to signify an increase in importance of the dipolar resonance structure of $CH_3ON$ relative to HON. By analogy, we would expect alkylated diazenes to possess a greater negative charge on the nitrene nitrogen than in $H_2NN$, with a corresponding increase in importance in the dipolar resonance structure. Hence, dialkyldiazenes should be more selective toward electrophilic olefins than diacyldiazenes, whose electron-withdrawing substituents would be expected to decrease the charge on the nitrene nitrogen and the importance of the dipolar resonance structure.[29] Our calculations support this argument in that the charge on the nitrogen in succinimidonitrene has been reduced from −0.24 to −0.17 and the bond index has been reduced from 1.87 to 1.44 relative to isodiimide.

Subsequent to this work, Peslak[30] reported *ab initio* molecular orbital studies of HON. He found that HON's bond angle was 112° compared to our 116° and the bond lengths were $R$ (N–O) = 1.32 and $R$ (H–O) = 0.98 Å as compared to our bond lengths of $R$ (N–O) = 1.20 and $R$ (H–O) = 1.05 Å. More signifi-

(28) M. Bandru and A. Foucaud, *C. R. Acad. Sci., Ser. C*, **270**, 104 (1970).
(29) Reference 1, p 363.
(30) J. Peslak, Jr., D. S. Klett, and C. W. David, *J. Amer. Chem. Soc.*, **93**, 5001 (1971).

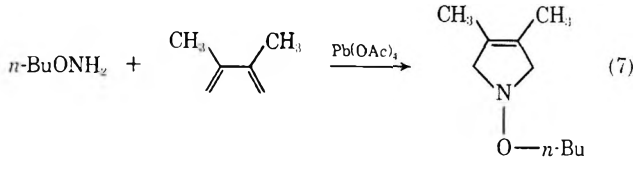
cantly, Peslak predicts the gross atomic charges as $H = 0.39$, $O = -0.50$, and $N = 0.10$. We have found that the nitrene nitrogen has the negative charge (Chart II).

The fact that only diazenes with electron-withdrawing groups add to olefins has been suggested to result from the negative substituent's effect of increasing the energy content and reactivity of the diazene without depriving it completely of its nucleophilic character.[29] Our calculations support the decrease in nucleophilic character, but, in view of the predictor equations, the stability of the diacyldiazene is not decreased; rather, it is increased. Thus we are led to postulate that the difference in reactivity between dialkyldiazenes and diacyldiazenes may result from the increased stability of the latter, allowing them to exist for sufficient time to react intermolecularly with the olefins.

In comparing HON and $H_2NN$, we note that the INDO calculations predict the diazene to be more stable than oxynitrene, implying that the former should be easier to generate. This is experimentally supported by the following data. *O*-benzyl-*N*-methanesulfonylhydroxylamine was stable in base at 100° for 18 hr,[13] whereas 1,1-dialkyl-2-benzenesulfonylhydrazines are decomposed in base at 110° within 15 min, yielding tetrazine, which can be reasonably postulated to arise through diazene intermediates.[9] The nitrene nitrogen of $H_2NN$ is significantly more negative than the nitrene nitrogen of HON, and we would expect this trend to be maintained in the alkylated species. Hence, it is reasonable to anticipate alkyloxynitrenes to be less selective toward electrophilic olefins than dialkyldiazenes.

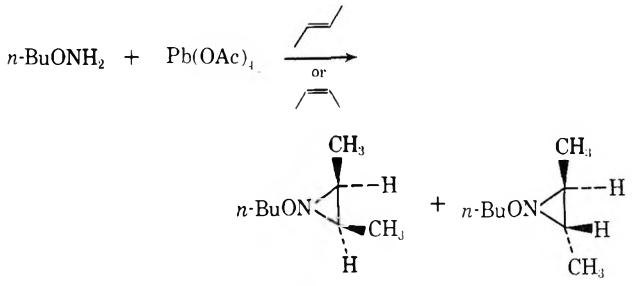
For oxynitrene, the singlet species was found to be the ground state, and therefore it should add to olefins stereospecifically. However, there has been only one report in which an oxynitrene has been postulated as an intermediate in an intermolecular trapping experiment.[11] Stereochemistry could not be deduced from this reaction (eq 4). Due to the lack of experimental evidence for the existence of free oxynitrene intermediates, it is somewhat difficult to draw any sound conclusions as to the electronic structure and properties of these compounds. Our INDO calculations simply predict these species to be bound in a singlet ground state, and less stable than the corresponding diazenes. This computed singlet character of oxynitrenes is entirely consistent with the postulated rearrangements shown in Scheme III.

Recent results[31] indicate that an oxynitrene is not the intermediate in the lead tetraacetate oxidation of O-substituted hydroxylamines. When *O*-*n*-butylhydroxylamine was oxidized by lead tetraacetate in the presence of 2,3-dimethyl-1,3-butadiene at −73°, the product was 1-*n*-butoxy-3,4-dimethyl-3-pyrroline



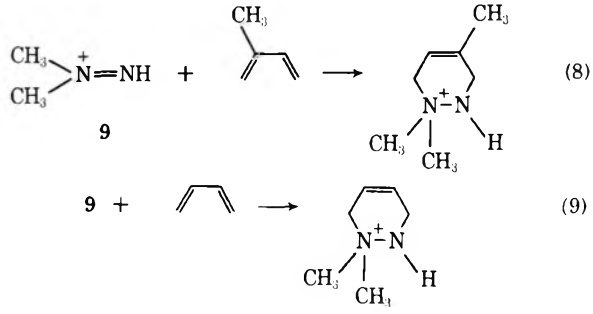

(7)

(eq 7). It was found that nonstereospecific addition occurred in the presence of *cis*- and *trans*-2-butene.

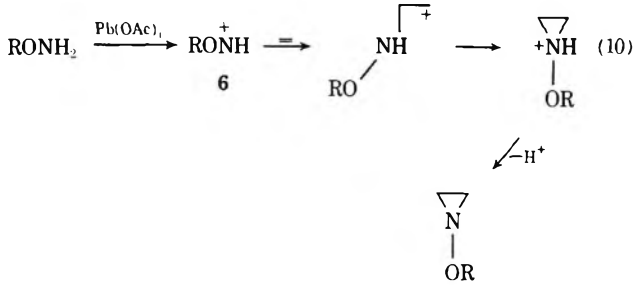



If the ground state of oxynitrene is indeed a singlet, as predicted by the INDO calculations, these reactions could not proceed *via* a free nitrene.

It is known that dialkyldiazenium ions add to olefins.[4b,32] When 1,1-dimethyldiazenium salt (**9**) was treated with isoprene or 1,3-butadiene at 0°, 1,4 addition occurred (eq 8 and eq 9, respectively). By anal-




ogy, it seems reasonable that the reactions of O-substituted hydroxylamines with lead tetraacetate in the presence of olefins could proceed through an oxynitrenium cation, **6** (eq 10), rather than the free nitrene, **2**.




To complete our study of the nitrenes, we carried out calculations on HSN and LiON. Geometry searches were carried out for HSN varying both the bond angle and bond distances and for LiON using Andrews' bond distances and varying the bond angle. Potential minima were found for both molecules. The binding energies and total energies are given in Table I. The atomic charge on the nitrogen of HSN is considerably larger relative to the other nitrenes studied.

The atomic charges found for LiON are in agreement with Peslak's results.[30] Both the oxygen and nitrogen have a negative charge and lithium has a positive charge. The theoretical bond angles (80 and

(31) This work is the subjest of a paper in preparation: F. A. Carey and L. J. Hayes.

(32) W. H. Urry, P. Szecoi, C. Ikoku, and D. W. Moore, *J. Amer. Chem. Soc.*, **86**, 2224(1964).

81°[30]) are in close agreement with the experimentally determined value (77.7°).

**Acknowledgment.**—The authors are grateful to Professor Frank A. Carey for helpful discussions during the course of the work and in the preparation of the manuscript. Financial support was provided by NSF Grant GP9550 to F. A. C. We also acknowledge a generous grant of computer time from the University of Virginia Computer Science Center.

# Base-Induced Decomposition of β-Nitroalkyl Nitrates

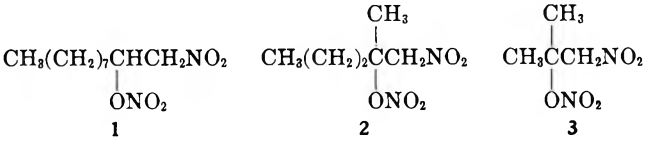
William M. Cummings* and Kenneth L. Kreuz

*Texaco Research Center, Beacon, New York 12508*

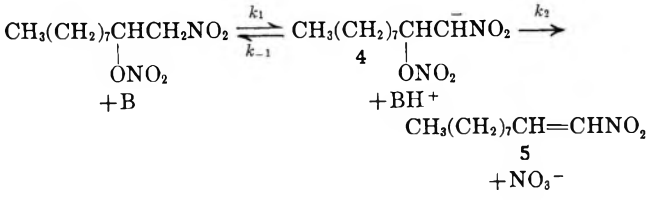
*Received June 30, 1972*

The elimination of nitric acid from β-nitroalkyl nitrates proceeds *via* an E1cb type of mechanism when the nitro and nitrate groups are attached to primary and secondary carbon atoms, respectively. Where the nitrate function is on a tertiary carbon, it has not been unequivocally shown that an E2 mechanism is operative, although the evidence points in that direction. Previous interpretation of the relative rate differences ascribed to 1,2-dinitrooctadecane, 1-nitro-2-octadecyl nitrate, and 1-nitro-2-octadecyl nitrite as differences in leaving group abilities may require reconsideration. Most likely these eliminations depend both on the leaving group abilities and on the acidity of the nitromethylene protons.

The elimination of the elements of nitric acid by a base from β-nitroalkyl nitrates has been known for many years. Usually, the β-nitroalkyl nitrate was studied as a component of a mixture formed from the addition of nitrogen dioxide to an olefinic linkage.[1] This mixture, consisting of β-nitroalkyl nitrate, β-nitro alcohol,[2] and 1,2-dinitroalkanes, yielded the corresponding nitro olefin. Siefert,[3] working with pure materials, found the following order of reactivity with pyridine: 1,2-dinitrooctadecane > 1-nitro-2-octadecyl nitrite > 1-nitro-2-octadecyl nitrate. These results were interpreted in terms of leaving group effects. With such structures the activating effect of the nitro group on proton release might figure importantly, along with leaving group effects, in the elimination process. This communication reports some preliminary results of a study of the pyridine-induced decomposition of β-nitroalkyl nitrates to nitro olefins and sheds some further light on the mechanism of the reaction. 1-Nitro-2-decyl nitrate (**1**), 1-nitro-2-methyl-2-pentyl nitrate (**2**), and 1-nitro-2-methyl-2-propyl nitrate (**3**) were chosen as model compounds.



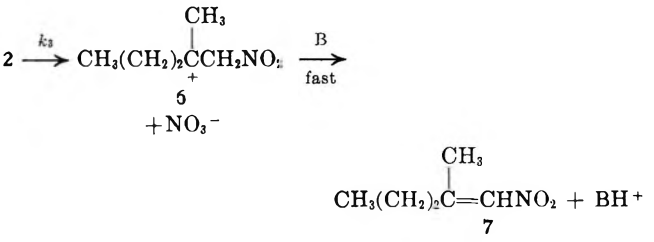
One possible reaction path would involve proton abstraction in an equilibrium step, followed by elimination of nitrate ion from the intermediate carbanion (E1cb type), *e.g.*, from **1**.



The steady-state approximation for such a process yields the rate expression of eq 1.

$$-\frac{d[1]}{dt} = \frac{k_1 k_2 [1][B]}{k_{-1}[BH^+] + k_2} \quad (1)$$

On the other hand, the nitro nitrate could lose nitrate ion in an unimolecular rate-determining step, forming a carbonium ion[4] which could eject a proton to form the nitro olefin (*e.g.*, from **2**).



Between these two extremes, there can exist intermediate situations in which bond-breaking at the nitro methylene carbon acts in concert with double bond formation and bond-breaking of the leaving group, leading to an E2 type mechanism (*e.g.*, for **1**).

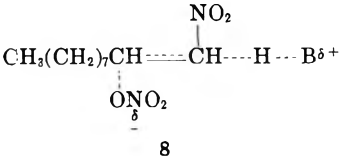


Table I gives the kinetic and product data for the decomposition of **1** and **2** in benzene and/or *m*-xylene in the presence of equimolar amounts of pyridine. For **1**, the product obtained in near quantitative yield is 1-nitro-1-decene (**5**), identified by infrared [strong absorption at 6.55 and 7.3 μ (vinyl $NO_2$ asymmetric and symmetric stretch, respectively)] and by nuclear magnetic resonance [a two-proton multiplet at δ 2.25 ($CH_2$-$CH$=$CHNO_2$), a one-proton multiplet at 6.9 ($CH_2$-$CH$=$CHNO_2$), and a one-proton multiplet at 8.25 ($CH_2CH$=$CHNO_2$)]. The reaction is second order, first order in both **1** and pyridine, through two half-lives. Pyridinium nitrate precipitates from solution

(1) V. V. Perekalin, "Unsaturated Nitro Compounds," Daniel Davy, New York, N. Y., 1964.

(2) Before treatment with base, the reaction mixture was hydrolyzed, converting the potentially explosive β-nitroalkyl nitrite to the β-nitro alcohol.

(3) W. K. Seifert, *J. Org. Chem.*, **28**, 125 (1963).

(4) For a discussion of a tertiary nitrate which reacts *via* an E1 process, see D. N. Kevill and R. F. Sutthoff, *J. Chem. Soc. B*, 3366 (1969).

TABLE I

DECOMPOSITION OF β-NITROALKYL NITRATES IN AROMATIC SOLVENTS

| Compd | Solvent | Initial concn, mol/l. β-Nitro nitrate | Initial concn, mol/l. Pyridine | Temp, °C | $k \times 10^4$, $M^{-1}$ sec$^{-1}$ [a] | Nitro olefin yield[b] |
|---|---|---|---|---|---|---|
| 1-Nitro-2-decyl nitrate | Benzene | 0.11 | 0.11 | 33.5 | 1.7 | 95% |
| | | 0.11 | 0.11 | 51.8 | 5.4 | |
| | | 0.11 | 0.11 | 60.0 | 10 | |
| | | 0.067 | 0.067 | 60.0 | 10 | |
| | | 0.13 | 0.13 | 60.0 | 11 | |
| 1-Nitro-2-methyl-2-pentyl nitrate | Benzene | 0.11 | 0.11 | 65.0 | 0.1 | 50% after one half-life |
| | *m*-Xylene | 0.11 | 0.11 | 97.0 | 4.5 | 68% after three half-lives at 97° |
| | | 0.11 | 0.11 | 114 | 14 | |
| | | 0.11 | 0.11 | 120 | 22 | |
| | | 0.22 | 0.22 | 97.0 | 4.5 | |

[a] Rate of reaction monitored by following the disappearance of the 7.8 and 11.6 μ infrared bands of the nitrate function ($-NO_2$ sym str and $-ONO_2$ str, respectively). The uncertainty of the rate constants is estimated at ±10%. [b] Compounds isolated by column chromatography using silica gel as the substrate with hexane as the eluting solvent.

TABLE II

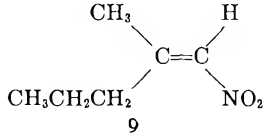
DECOMPOSITION OF β-NITRO NITRATES IN THE PRESENCE OF DEUTERIUM OXIDE AND PYRIDINE[a]

| Compd | Concn, *M* | Solvent | Temp, °C | Time, hr | Conversion, % | Deuterium incorpd into nitro olefin |
|---|---|---|---|---|---|---|
| 1-Nitro-2-decyl nitrate | 0.11 | 80% $CH_3CN$–20% $D_2O$ | 75 | 0.5 | 100 | 50% (nmr) at the 1 position |
| 1-Nitro-1-decene | 0.11 | | 75 | 2.0 | | No (<5%) deuterium incorporation |
| | 0.11[d] | | 75 | 1.0 | | |
| 1-Nitro-2-methyl-2-propyl nitrate | 0.11 | | 75 | 2.0 | 80 | 7% (mass spectrum)[b] |
| | 0.11 | | 75 | 4.0 | 100 | 25% (nmr) |
| | 0.11 | | 25 | | 60 | No deuterium (nmr) |
| 1-Nitro-2-methyl-1-propene | 0.11 | | 75 | 2.0 | | 33% (nmr) deuterium incorporation |

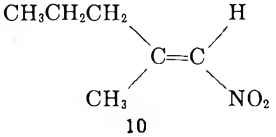
[a] Pyridine was present in the same molar quantities as the β-nitro alkyl nitrates. [b] The mass spectrum of 1-nitro-2-methyl-1-propene is complicated by a large M + 1 peak. The presence of an ion–molecule process was confirmed by monitoring the ratio M/(M + 1) peak as a function of sample size. As sample increased, M/(M + 1) decreased. [c] Some isomerization to the unconjugate disomer 1-nitro-2-methyl-2-propene occurs as evidenced by ir absorption at 6.4 μ and nmr absorptions at δ 5.0. [d] 0.11 *M* pyridinium nitrate was present, no pyridine was present.

from the outset of the experiment. The temperature coefficient is small with an apparent energy of activation of *ca.* 12 kcal.

1-Nitro-2-methyl-2-pentyl nitrate (**2**) decomposes more slowly than **1** to give 1-nitro-2-methyl-1-pentene (**7**) having strong infrared absorption at 6.55 and 7.3 μ. The nuclear magnetic resonance spectrum (three allylic methyl hydrogens at δ 1.95 and three allylic hydrogens at 2.55) shows it to be a mixture of cis and trans isomers (**9**, **10**).




**9**




**10**

In benzene at 65°, only **9** and **10** are formed when the decomposition is limited to one half-life. At higher temperatures (~100°) after complete decomposition of **2**, **9** and **10** are isolated in only 68% yield. The remaining material is a viscous, resinous substance. Since at these temperatures pyridinium nitrate begins to decompose, this resin formation is attributed to its oxidizing action. As with **1**, the initial reaction is second order, with an indicated temperature coefficient ($E_a$) of *ca.* 18 kcal.

When the decomposition of **1** and **2** was carried out in the more polar solvent, acetonitrile, the rates of decomposition were observed to increase significantly. Both followed approximate second-order kinetics through the first half-life. For **1** at 33° and for **2** at 65°, the indicated specific rate constants were $2.9 \times 10^{-3}$ and $1.0 \times 10^{-3}$ $M^{-1}$ sec$^{-1}$. Subsequent decomposition was slower than expected for a straightforward second-order process.[5] No precipitate was formed in these experiments.

These results indicate that the β-nitroalkyl nitrates reacted initially *via* an apparent bimolecular process. In all the solvents used in the study (benzene, *m*-xylene, acetonitrile, acetonitrile–deuterium oxide), **1** always reacted faster than **2**, arguing against the possibility that both **1** and **2** are reacting *via* a concerted E2 type process. If such were the case, **2** might have been expected to react faster because of transition state stabilization by the additional alkyl group.[6] An E1cb type process is, however, a reasonable possibility for both **1** and **2**. Carbanion mechanisms involving an initial equilibrium step can usually be detected by using as a reaction medium some compound which contains labile deuterium atoms. The intermediate carbanion abstracts the labile deuterium while reverting to starting material so that deuterium becomes incorporated into the latter and thence into the final product species.

Table II gives the results obtained when **1** and **3** were decomposed in acetonitrile in the presence of deuterium oxide. Deuterium incorporation was followed by nuclear magnetic resonance measurements. Compound **3** was chosen instead of **2** to simplify the nuclear

(5) Successive half-lives for I at 65° were 19 and 57 min, where $[NN]_i = [B]_i = 0.11$ *M*.

(6) D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1962, p 62.

magnetic resonance spectra. Isomers such as **9** and **10** caused the spectra to be somewhat complex and difficult to analyze.

When **1** was completely decomposed in the presence of deuterium oxide, the nitro olefin formed (**5**) was found to contain deuterium at the 1 position (one-proton multiplet at δ 6.9 reduced in intensity to 50%). Subjecting unlabeled **5** to reaction conditions (see Table II) caused no deuterium (within limits of the nmr) to be incorporated into the molecule. This excludes the possibility of a subsequent equilibration with the nitro olefin and shows that deuterium is being incorporated into the molecules as the molecules are reacting with the base. An E1cb type mechanism is most likely operative in this case.

For an E1cb type of mechanism to follow good second-order kinetics through two half-lives (Table I, benzene data) is unusual. Normally as $BH^+$ increases (eq 1) the rate decreases. However, as noted earlier, pyridinium nitrate precipitates immediately from benzene or xylene solution. The concentration of $BH^+$ must therefore be constant and very small,[7] compared to the reactant concentrations used, throughout the measured reaction times. This accounts for the observed good second-order kinetics for these solvents, with the reaction rate constant approximating $k_1$.

$$-\frac{d[1]}{dt} = k_1[1][\text{pyridine}]$$

When **3** was completely decomposed in the presence of deuterium oxide at 75°, the nitro olefin isolated (**11**)

$$(CH_3)_2C{=}CHNO_2$$
**11**

contained 25% deuterium at the 1 position. However, when unlabeled **11** was subjected to reaction conditions, 33% deuterium was incorporated into the molecule. Interruption of the decomposition of **3** at 80% conversion revealed that only 7% (mass spectra) deuterium had been incorporated into the nitro olefin. When **3** was decomposed at 25° (60% conversion) no deuterium could be detected (within the limits of nmr) in either recovered **3** or the product, 1-nitro-2-methyl-1-propene. Apparently little if any deuterium was incorporated into the molecule during decomposition, most if not all being incorporated after the formation of the nitro olefin.

Because of the sensitivity limits of the analytical method, it can not be unequivocally said that the reaction does not proceed by an E1cb type process. If it does proceed in this manner, the results show that during the first half-life, at least, $k_1[BH^+]$ is small with respect to $k_2[An^-]$ (that is, nitrate is being eliminated faster than deuterium is being incorporated), and the mechanism is approaching the E2 type.

Table III shows literature data[8] for the effect of β-methyl substitution upon proton removal from a series of nitro alkanes. Substitution of the β hydrogen by a methyl group causes a decrease in the rate of proton removal from the nitromethylene carbon by a factor near 2. Proton removal from **2** or **3** should be slower than from **1** since they differ by this β substitution. This decrease in $k_1$, coupled with the possibility that $k_2$ may be larger for **2** or **3** (since nitrate is leaving from a tertiary center), makes reasonable the tentative conclusion that the E2 mechanism is favored by **2** (or **3**), while **1** decomposes by E1cb.

Table III
Rate of Proton Removal from Nitro Alkanes

| Nitro alkane | $k_1$, $M^{-1}$ min$^{-1}$ |
|---|---|
| $CH_3NO_2$ | 1026 |
| $CH_3CH_2NO_2$ | 354 |
| $CH_3CH_2CH_2NO_2$ | 195 |

A similar effect, though less pronounced, has been seen in the reactions of α- and β-methyl substituted β-phenylethyl tosylates and bromides with potassium *tert*-butoxide in *tert*-butyl alcohol and sodium ethoxide in ethanol.[9] These compounds have been shown to develop less carbanion character in their transition states in elimination reactions than those of β-phenylethyl tosylates and bromides.

## Experimental Section

The infrared spectra were obtained with a Perkin-Elmer 137B double beam recording spectrophotometer using thin films on sodium chloride disks, or differentially in solution in 0.1-mm sodium chloride cells. Nuclear magnetic resonance spectra were determined with a Varian Associates H-100 spectrometer at 100 MHz with tetramethylsilane as the internal standard. Mass spectra were determined with a CEC 21-104 mass spectrometer.

**General Preparation of β-Nitroalkyl Nitrates *via* β-Nitroalkyl Peroxynitrates.**[10] **A. β-Nitroalkyl Peroxynitrates.**—To 100 ml of a 1.3 *M* carbon tetrachloride solution of 1-alkene at 0° was added 8.0 ml (0.13 mol) of dinitrogen tetroxide over a period of 6 hr. The addition of the dinitrogen tetroxide was carried out by allowing a stream of oxygen (56 ml/min) to pass over the liquid dinitrogen tetroxide into the reaction vessel. After the dinitrogen tetroxide had been added, oxygen was allowed to flow through the reaction solution until the solution became colorless. Solution infrared showed that the β-nitroalkyl peroxynitrate has formed (strong absorptions at 5.8, 6.4, and 7.3 μ).

**B. β-Nitroalkyl Nitrates.**—From the above solution the solvent was removed *in vacuo* at 20° and 100 ml of new solvent was added. This solution was chilled to −10° and 0.13 mol of nitric oxide was added by passing nitric oxide through the solution at a flow rate of 60.8 ml/min. After two additions, the solution was kept at −10° for 30 min and then allowed to warm to room temperature. The solvent was then removed, giving the β-nitroalkyl nitrate in near quantitative yield. These β-nitroalkyl nitrates were purified by chromatography on silica gel columns using hexane–methylene chloride (90:10) mixtures as the eluting solvent.

**Kinetic Experiments.**—Equimolar solutions of β-nitroalkyl nitrates and pyridine were mixed together and then the unstirred solutions were heated to the desired temperature. The decompositions of the β-nitroalkyl nitrates were followed by monitoring the disappearance of the 6.1, 7.8, and 11.6 μ infrared absorption bands. The solutions of β-nitroalkyl nitrates followed Beer's law in the concentration ranges studied (up to 0.22 *M*). The temperatures were maintained at ±0.5°. Aliquots were withdrawn at timed intervals and their spectra were recorded differentially in 0.1-mm sodium chloride cells *vs.* the appropriate solvent. A base line, straddling the peak, technique was used to measure the absorbances of the band being monitored.[11] The rate constants were reproducible within ±3%.

Isolation of the decomposition products was carried out by first filtering the precipitated pyridinium nitrate and then removing the reaction solvent. The crude product was chromatographed on silica gel using hexane as an eluent. In the cases

(7) The measured solubility of pyridinium nitrate in benzene at 25 and 65° was found to be ~$10^{-4}$ and $10^{-3}$ mol/l., respectively.

(8) A. T. Nielsen, "The Chemistry of the Nitro and Nitroso Groups," Part 1, H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 368.

(9) C. H. DePuy, D. L. Storm, J. T. Frey, and C. G. Naylor, *J. Org. Chem.*, **35**, 2746 (1970).

(10) D. R. Lachowicz and K. L. Kreuz, *ibid.*, **32**, 3885 (1967); U. S. Patent 3,282,983 (1966).

(11) H. Morgan, R. M. Sherwood, and T. A. Washall, *Anal. Chem.*, **38**, 1009 (1966).

where pyridinium nitrate did not precipitate, the solvent was reduced to one-half its original size and four times that volume of ether was added. This solution was extracted three times with equal volumes of water and the ethereal layer was then separated and dried over sodium sulfate. The crude residue left after the ether was removed was chromatographed on silica gel using hexane as an eluent.

Inspection of all the crude reaction products was done by infrared and nuclear magnetic resonance spectra. The amount of deuterium incorporated was determined from nuclear magnetic resonance spectra or from mass spectra. 1-Nitro-2-methyl-2-pentyl nitrate, 1-nitro-2,4,4-trimethyl-2-pentyl nitrate,[12] and 1-nitro-2-methyl-2-propyl nitrate[13] have been described previously, as has 1-nitro-2-methyl-1-propene.[14] The elemental analysis for 1-nitro-1-decene and 1-nitro-2-methyl-1-pentene are given below.

| | | C | H | N |
|---|---|---|---|---|
| $C_{10}H_{19}NO_2$ | Calcd | 64.9 | 10.4 | 7.57 |
| | Obsd | 64.5 | 10.5 | 7.30 |
| $C_6H_{11}NO_2$ | Calcd | 55.8 | 8.60 | 10.9 |
| | Obsd | 55.4 | 9.00 | 10.9 |

**Registry No.**—**1**, 36601-57-7; **2**, 35223-51-9; **3**, 14202-69-8; **5**, 36601-60-2; **9**, 36601-61-3; **10**, 36601-62-4; **11**, 1606-30-0.

(12) J. M. Larkin and K. L. Kreuz, *J. Org. Chem.*, **37**, 3079 (1972).
(13) N. Levy, C. W. Scaife, and A. E. Wilder-Smith, *J. Chem. Soc.*, 52 (1948).
(14) A. Lambert and A. Lowe, *ibid.*, 1517 (1947).

# The Use of an α-Fluorine Substituent as a Transition State Probe in Base-Catalyzed Nitrous Acid Eliminations

LLOYD A. KAPLAN* AND NICHOLAS E. BURLINSON

*Advanced Chemistry Division, U. S. Naval Ordnance Laboratory, Silver Spring, Maryland 20910*

*Received April 4, 1972*

The results of a study of the kinetics and mechanism of the reaction of 4,4,4-trinitrobutyronitrile and 4,4-dinitro-4-halobutyronitriles with base have shown that the isolated products are derived from an extremely reactive 1,1-dinitro- or 1-halo-1-nitroethylene intermediate. The α-fluorine effect has been utilized as a transition state probe to show that the mechanism by which the olefin intermediate forms is a nonreversible, second-order carbanion β elimination of the elements of nitrous acid.

The reaction of 1,1,1-trinitroethyl compounds with bases[1-6] has been viewed as yielding a 1,1-dinitroethylene intermediate **1**.[1] The fate of this reactive intermediate depends upon the nature of the substituent attached to the carbon α to the dinitromethyl group (eq 1). When R = $CH_2Y$, where Y is a con-

$$\underset{\mathbf{1}}{C(NO_2)_2{=}CHR} + Nu^- \xrightarrow{R = CH_2Y} \underset{\mathbf{2}}{{}^-C(NO_2)_2CH{=}CHY} \qquad (1)$$

$$\searrow^{R = H \text{ or alkyl}}$$

$$\underset{\mathbf{3}}{{}^-C(NO_2)_2CHRNu}$$

$$Y = CO_2Me, CN, NO_2, SO_2Me$$
$$Nu^- = CN^-, OR^-, \text{amines}, OH^-$$

jugatively electron-withdrawing substituent, the olefin **1** loses an α-methylene proton to form the planar[7] carbanion **2**. When this path is not available, nucleophilic addition to the double bond occurs to form the adduct **3**. Though the olefin **1** has never been isolated from these base-catalyzed eliminations, its rate of formation might be expected to be slow relative to subsequent reactions. Thus, a combination of kinetic and trapping experiments should enable us to determine if **1** is the precursor of **2** and **3**.

We also planned to utilize the α-fluorine effect[8,9] as a probe to determine the structure of the transition state for this nitrous acid elimination reaction (eq 2).

$$\underset{\mathbf{4}}{ZC(NO_2)_2CH_2CH_2Y} + OH^- \longrightarrow \underset{\mathbf{5}}{ZC(NO_2){=}CHCH_2Y} \qquad (2)$$

$$Y = CN;\ Z = NO_2, F, \text{and } Cl$$

If the formation of **5** requires concerted C–H and C–$NO_2$ bond breaking in the transition state, then the γ carbon atom, $ZC(NO_2)_2$–, has more s character in the transition state than in the ground state and $\Delta H^*$, but not necessarily $\Delta F^*$,[8] for Z = F should be larger than for Z = $NO_2$ or Cl.[8,9] Alternatively, if only carbanion formation occurs in the rate-determining step,[10] then the hybridization of the γ carbon atom will be the same in the ground and transition states and $\Delta H^*$[8] for Z = F and $NO_2$ should be essentially the same.[11] The twofold effect of the enhanced acidity of the β hydrogen atoms due to the strongly electron-withdrawing $ZC(NO_2)_2$ function and the presence of a good leaving group, nitro departing as resonance-stabilized nitrite ion, might be expected to make the elimination of nitrous acid from the substrates **4** proceed by a nonreversible carbanion mechanism rather than an E2 or a reversible E1cB mechanism.

## Results and Discussion

**The Overall Reaction.**—Prior to making kinetic measurements, we carefully investigated the reaction of the substrates **4** with hydroxide. Since they have

(1) L. Zeldin and H. Shechter, *J. Amer. Chem. Soc.*, **79**, 4708 (1957).
(2) J. Meisenheimer and M. Schwarz, *Chem. Ber.*, **39**, 2546 (1906).
(3) J. Meisenheimer, *ibid.*, **36**, 434 (1903).
(4) M. J. Kamlet and J. C. Dacons, *J. Org. Chem.*, **26**, 3005 (1961).
(5) L. A. Kaplan, *ibid.*, **29**, 2256 (1964).
(6) M. J. Kamlet, J. C. Dacons, and J. C. Hoffsommer, *ibid.*, **26**, 4881 (1961).
(7) L. A. Kaplan, N. E. Burlinson, W. B. Moniz, and C. Poranski, *Chem. Commun.*, 140 (1970).
(8) L. A. Kaplan and H. B. Pickard, *ibid.*, 1500 (1969); L. A. Kaplan and H. B. Pickard, *J. Amer. Chem. Soc.*, **93**, 3447 (1971).
(9) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967).
(10) For a description of the various mechanisms for base-catalyzed β eliminations, see F. G. Bordwell, M. M. Vestling, and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5950 (1970), and references cited therein.
(11) Since the $\sigma^*$ values for $FC(NO_2)_3$ and $C(NO_2)_4$, 4.4[12] and 4.5,[13] are about equal, large differences in $\Delta H^*$ cannot be attributed to differences in Cβ–H bond strengths.
(12) L. A. Kaplan and H. B. Pickard, *J. Org. Chem.*, **35**, 2044 (1970).
(13) J. Hine and W. C. Bailey, *ibid.*, **26**, 2098 (1961).

two sites, $C_\beta H_2$ and $C_\alpha H_2$, bearing acidic protons, the possibility existed that the desired reaction would be complicated by a retrograde Michael reaction yielding the Z-substituted dinitromethide ion and acrylonitrile.[14] When **4**, Z = $NO_2$, was allowed to react with hydroxide at spectrophotometric concentrations, a comparison of the spectrum of the reaction mixture with that of authentic **7** indicated the presence of a second species absorbing between 350 and 380 nm. After subtraction of the absorbance contribution of **7** from the spectrum of the reaction mixture, the residual absorbance peaked at 362 nm. The position of this maximum is coincident with that of dinitromethide ion.[15] The formation of dinitromethide ion together with **7** can be rationalized by the following sequence in which the

$$C(NO_2)_3CH_2CH_2CN + OH^- \xrightarrow{-HNO_2} C(NO_2)_2{=}CHCH_2CN \xrightarrow{-H\alpha^+} {}^-C(NO_2)_2CH{=}CHCN \quad (3)$$

(6 → 7; OH⁻ / 8)

$$^-C(NO_2)_2CHOHCH_2CN \longrightarrow HC(NO_2)_2^- + OCHCH_2CN$$

addition product **8** dissociates to form dinitromethide ion.[16]

From the stoichiometry of the reaction (eq 3), there should be a 1:1 correspondence between the concentrations of **7** plus dinitromethide ion and nitrite ion. Several reaction mixtures were assayed for nitrite ion as well as the dinitrocarbanion species formed. The data are presented in Table I.

TABLE I

REACTION OF $4.98 \times 10^{-5}$ *M* $C(NO_2)_3CH_2CH_2CN$ WITH $OH^-$ IN WATER AT 25°

| Buffer[a] | pH | $10^5[7]$[b] | $10^5[HC(NO_2)_2^-]$[b] | $10^5[NO_2^-]$[c] |
|---|---|---|---|---|
| B, 0.01/0.04 | 9.66 | 4.14 | 0.52 | 5.40 |
| B, 0.015/0.035 | 9.46 | 4.12 | 0.58 | 5.36 |
| B, 0.005/0.045 | 9.79 | 4.12 | 0.58 | 5.36 |
| C, 0.007/0.018 | 9.54 | 3.91 | 0.74 | 5.30 |

[a] B = Borax–hydroxide, C = bicarbonate–hydroxide, [HA]/[A⁻] in *M*. [b] Calculated from absorbance measurements at 320 nm $\lambda_{max}$ **7**, and 362, $\lambda_{max}$ $HC(NO_2)_2^-$. Average [7 + $HC(NO_2)_2^-$] = $4.68 \pm 0.02 \times 10^{-5}$ *M*. [c] Average $[NO_2^-] = 5.36 \pm 0.03 \times 10^{-5}$ *M*.

Inspection of the data shows both the concentrations of nitrite and **7** plus $HC(NO_2)_2^-$ to be remarkably constant. However, the average value of the sum of the carbanion concentrations is 6% less than theoretical, $4.98 \times 10^{-5}$ *M*, and the average value of the nitrite concentration is about 8% greater. As both **7** and dinitromethide ion are stable in the reaction medium, either 4,4,4-trinitrobutyronitrile or the intermediates **6** or **8** denitrosate under these conditions. Nucleophilic attack on the trinitromethyl group of the substrate molecule by hydroxide ion can be ruled out, as this would produce nitrate rather than nitrite together with 4,4-dinitrobutyronitrile.[1,17] Since the formation of **6** will be shown to be rate determining, partitioning it among several side reactions will not affect the measurement of its specific rate of formation.

In a similar fashion, **4**, Z = F or Cl, reacted with hydroxide ion to form the 4-fluoro-4-nitro and 4-chloro-4-nitro analogs of **7**. On a synthetic scale, it was not possible to isolate the potassium salts of these carbanions, as they were not stable. However, they were formed quantitatively at spectrophotometric concentrations, since a mole for mole correspondence between nitrite ion formed in the reaction and the initial concentration of halodinitrobutyronitrile was obtained. The absorptions of these carbanions in the ultraviolet were consistent with structures analogous to **7** (Table II).

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA FOR $^-ZC(NO_2)CH{=}CHY$[a]

| Z | Y = CN | Registry no. | Y = $CO_2^-$ | Registry no. |
|---|---|---|---|---|
| Cl | 342 (13,800)[b] | 36529-35-8 | 322 (16,400)[c] | 36488-77-4 |
| F | 335 (23,000)[b] | 36529-36-9 | 317 (19,500)[c] | 36488-78-5 |
| $NO_2$ | 320 (19,300)[c,d] | 26881-30-1 | 313 (16,000)[c,e] | 36529-38-1 |

[a] $\epsilon$ values in parentheses. [b] In 0.2 *M* sodium hydroxide, $\epsilon$ values based on the concentration of halodinitrobutyronitrile. [c] In 0.01 *M* sodium hydroxide. [d] Long wavelength maximum at 395 nm ($\epsilon$ 9800). [e] Long wavelength maximum at 410 nm ($\epsilon$ 8300).

Corroboration of these structural assignments was obtained from the reaction products of the corresponding acids **4**, Y = $CO_2H$, with hydroxide ion. Isolable dipotassium salts of 4-fluoro-4-nitro- and 4-chloro-4-nitro-2-butenoic acids were obtained. The nmr spectra of these salts (Table III) are of the AB or the ABX, X = F, type with $J_{AB}$ = 15–16 Hz. The magnitude of $J_{AB}$ is consistent with a trans configuration of the substituents attached to the double bond. The assignments of the lines in Table III for Z = Cl and $NO_2$ were made by comparison with the positions of the lines in the spectrum of Z = F. For this carbanion, the upfield multiplet had $J$ = 1.5 Hz. The smaller $J_{HF}$ value would be expected for the longer range $J_{HAF}$ coupling.

TABLE III

100-MHZ NMR SPECTRA OF $^-ZC(NO_2)CH_BH{=}CH_ACO_2^-$ IN $D_2O$[a]

| Z | $\delta_{HA}$ | $\delta_{HB}$ |
|---|---|---|
| F | 6.362 6.380, 6.517,6.532 | 7.497, 7.650, 7.730, 7.886 |
| Cl | 6.464, 6.615 | 8.060, 8.213 |
| $NO_2$ | 6.884 7.040 | 8.106 8.263 |

[a] External TMS reference in capillary insert, 30°.

**Kinetics of the Reaction.**—Reaction rates for the three nitrile substrates **4** were measured under pseudo-first-order conditions either in excess sodium hydroxide or in buffer solutions of an appropriate pH. The rate of appearance of the 4-Z-4-nitro-2-butenenitrile elimination product was followed in the ultraviolet (Table II). Pseudo-first-order rate constants were evaluated from the slopes of plots of log ($OD_\infty - OD_t$) *vs.* time. These plots were found to be linear for at least 3 half-

(14) The reaction of **4**, Y = $CO_2Me$ and Z = $NO_2$, with bases produced trinitromethide ion and the carbanion $^-C(NO_2)_2CH_2CHOHCO_2Me$ together with **2**, Y = $CO_2Me$. See L. A. Kaplan and D. J. Glover, *J. Amer. Chem. Soc.*, **88**, 84 (1966).

(15) M. J. Kamlet and D. J. Glover, *J. Org. Chem.*, **27**, 537 (1962).

(16) P. Duden and G. Ponndorf, *Chem. Ber.*, **38**, 203 (1905); L. Herzog, M. H. Gold, and R. D. Geckler, *J. Amer. Chem. Soc.*, **73**, 749 (1951); H. Feuer, G. B. Bachmann, and W. May, *ibid.*, **76**, 5129 (1954); T. N. Hall, *J. Org. Chem.*, **29**, 3587 (1964).

(17) D. J. Glover, *J. Phys. Chem.*, **74**, 21 (1970).

TABLE IV

REACTION OF $ZC(NO_2)_2CH_2CH_2CN$ WITH HYDROXIDE ION, $\mu = 0.1$

| [HA][a] | [A⁻] | pH | $10^5[OH^-]$[b] | $k_2$, $M^{-1}$ sec$^{-1}$ |
|---|---|---|---|---|
| | | Z = $NO_2$, $T$ = 25° | | |
| C, 0.010 | 0.015 | 10.13 | 22.1 | 24.0 |
| C, 0.015 | 0.010 | 9.79 | 10.1 | 23.7 |
| C, 0.020 | 0.005 | 9.37 | 3.85 | 23.3 |
| C, 0.034 | 0.016 | 9.67 | 7.67 | 24.6 |
| B, 0.020 | 0.080 | 9.70 | 8.22 | 23.1 |
| B, 0.015 | 0.035 | 9.44 | 4.52 | 23.3 |
| B, 0.010 | 0.040 | 9.66 | 7.50 | 23.6 |
| B, 0.005 | 0.045 | 9.79 | 10.1 | 24.0 |
| B, 0.0025 | 0.0225 | 9.84 | 11.4 | 24.3 |
| | | | Average | 23.8 ± 0.4[f] |
| | | Z = $NO_2$, $T$ = 40° | | |
| C, 0.020 | 0.005 | 9.250 | 8.22 | 95.8 |
| C, 0.020 | 0.005 | 9.278 | 8.77 | 95.5 |
| C, 0.020 | 0.005 | 9.301 | 9.25 | 91.0 |
| C, 0.015 | 0.010 | 9.667 | 21.5 | 91.4 |
| C, 0.015 | 0.010 | 9.690 | 22.7 | 90.1 |
| C, 0.010 | 0.015 | 9.944 | 40.6 | 96.6 |
| C, 0.010 | 0.015 | 9.986 | 44.8 | 93.6 |
| B, 0.045 | 0.005 | 8.178 | 0.697 | 100 |
| B, 0.040 | 0.015 | 8.622 | 1.94 | 98.7 |
| B, 0.040 | 0.010 | 8.410 | 1.19 | 99.4 |
| B, 0.030 | 0.020 | 8.800 | 2.92 | 96.7 |
| B, 0.030 | 0.020 | 8.795 | 2.88 | 98.9 |
| | | | Average | 95.6 ± 2.8[f] |
| | | Z = F, $T$ = 25° | | |
| | | 11.496 | 514 | 0.198 |
| | | 11.505 | 525 | 0.183 |
| P, 0.0022 | 0.0103 | 11.585 | 631 | 0.187 |
| | | 11.657 | 745 | 0.200 |
| | | 11.706[c] | 834 | 0.191 |
| | | 11.706[d] | 834 | 0.193 |
| | | 11.716 | 853 | 0.189 |
| | | 11.716[e] | 853 | 0.191 |
| | | 11.726 | 873 | 0.190 |
| | | 11.798 | 1030 | 0.190 |
| | | 11.807 | 1050 | 0.189 |
| | | 11.826 | 1100 | 0.181 |
| | | | Average | 0.190 ± 0.004 |
| | | Z = F, $T$ = 40° | | |
| P, 0.020 | 0.005 | 10.665 | 214 | 0.813 |
| P, 0.020 | 0.005 | 10.657 | 210 | 0.818 |
| P, 0.015 | 0.010 | 11.022 | 486 | 0.793 |
| P, 0.015 | 0.010 | 11.028 | 493 | 0.780 |
| P, 0.015 | 0.010 | 11.026 | 491 | 0.783 |
| C, 0.010 | 0.015 | 10.129 | 62.2 | 0.791 |
| | | | Average | 0.796 ± 0.013 |
| | | Z = Cl, $T$ = 25° | | |
| P, 0.0005 | 0.0102 | 11.685 | 794 | 0.111 |
| P, 0.0023 | 0.0102 | 11.420 | 432 | 0.114 |
| | | 11.838 | 1130 | 0.113 |
| | | 12.019 | 1710 | 0.118 |
| | | 12.019[e] | 1710 | 0.114 |
| | | | Average | 0.114 ± 0.002 |
| | | Z = Cl, $T$ = 40° | | |
| P, 0.020 | 0.005 | 10.652 | 208 | 0.615 |
| P, 0.015 | 0.010 | 11.011 | 474 | 0.620 |
| P, 0.010 | 0.015 | 11.208 | 746 | 0.621 |
| P, 0.010 | 0.015 | 11.243 | 809 | 0.620 |
| C, 0.003 | 0.022 | 10.425 | 123 | 0.631 |
| | | | Average | 0.616 ± 0.004 |

[a] C = $HCO_3^-/CO_3^{2-}$, B = $H_3BO_3/H_2BO_3^-$, P = $HPO_4^{2-}/PO_4^{3-}$. No entry indicates that an appropriate aliquot of 0.10 $M$ sodium hydroxide was used in place of the buffer. Substrate concentrations are $10^{-4}$ to $5 \times 10^{-5}$ $M$. [b] p$K$ water at ionic strength = 0.1; 13.785 (25°) and 13.335 (40°). H. S. Harned and W. J. Hamer, *J. Amer. Chem. Soc.*, **55**, 2194 (1933). [c] NaBr used instead of $NaClO_4$ to adjust ionic strength to 0.1. [d] As in *c* but NaCl used. [e] As in c but $Na_2S_2O_3$ used. [f] Statistically corrected for three nitro groups; $k_2^{25°}$ = 15.9 ± 0.3 $M^{-1}$ sec$^{-1}$ and $k_2^{40°}$ = 63.7 ± 1.9 $M^{-1}$ sec$^{-1}$.

lives and were generally good quality straight-line plots for 5 half-lives. For some of the kinetic runs using 4,4,4-trinitrobutyronitrile as the substrate, the actual concentrations of the carbanion **7** and dinitromethide ion were calculated from the change in absorbance at 320 and 362 nm with time. Rate constants evaluated from either product species and the initial concentration of 4,4,4-trinitrobutyronitrile were found to be identical with those obtained by graphing log ($OD_\infty$ − $OD_t$) *vs.* time. Although the values of the first-order constants varied with the hydroxide concentration, dividing them by the hydroxide concentration gave $k_2$ (Table IV), which is constant over the range of hydroxide concentrations studied. These observations are described by the rate expression eq 4.

$$-d[4]/dt = k_2[4][OH^-] \quad (4)$$

The first-order dependency of the rate on the hydroxide concentration indicated that $k_2$ described the specific rate of nitrous acid elimination from the substrates **4**. Additional evidence for this conclusion came from the results of trapping experiments. From the data in Table I, about 10% of the product formation occurs by nucleophilic addition to the double bond of **6** (eq 3). If hydroxide is acting as a nucleophile to form **8** and a base to form **7**, then generating the olefin **6** in the presence of thiosulfate ion at a concentration equal to or greater than the hydroxide concentration should divert all of **6** to the addition path, as thiosulfate ion is about 150 times more reactive as a nucleophile[18] and about $10^{12}$ times weaker a base than hydroxide.[19]

When 4,4,4-trinitrobutyronitrile was treated with hydroxide ($HCO_3^-/CO_3^{2-}$) in the presence of excess thiosulfate ion, the ultraviolet spectrum of the reaction mixture exhibited an absorption maximum at 368 nm that increased with time.[20] The position of this maximum is consistent with **9**,[21] the product ex-

$$\underset{\mathbf{6}}{C(NO_2)_2{=}CHCH_2CN} + S_2O_3^{2-} \longrightarrow \underset{\mathbf{9}}{{}^-C(NO_2)_2CHCH_2CN}\ (S_2O_3^-) \quad (5)$$

(18) Using methyl bromide as the reference substrate: C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

(19) If one compares the p$K$ of $HS_2O_3^-$, ~2 [F. M. Page, *J. Chem. Soc.*, 1719 (1953)], and water.

(20) Neither 4,4-dinitro-4-fluoro- nor 4,4,4-trinitrobutyronitrile reacted with 1 $M$ thiosulfate ion at pH's less than 7. Even in nonalkaline media, the 4-chloro derivative was reduced to 4,4-dinitrobutyrontrile. Similar changes in the site of attack of nucleohiles have been observed previously: L. A. Kaplan in "The Chemistry of the Nitro and Nitroso Groups," Vol. II, H. Feuer, Ed., Wiley, New York, N. Y., 1970, p 321; *cf.* ref 1. With thiosulfate ion at pH ~12, **4**, Z = F, yielded only the 4-fluoro-4-nitro analog of **7**. The inability of the fluoro derivative to form an addition product of the type **9** can be attributed to the reduced susceptibility of the double bond in **5**, Z = F, to nucleophilic attack on replacing the conjugatively electron-withdrawing nitro group by fluorine.

(21) Carbanions of the general structure $^-C(NO_2)_2CHZCH_2Y$, Y = CN, $SO_2Me$, $CO_2Me$, etc., and Z = substituent with unshared p pairs as OMe. have absorption maxima between 360 and 370 nm.[15]

pected from the addition of thiosulfate ion to the olefin **6**. The absorbance at 368 nm went through a maximum, and concurrent with the decrease in absorption at 368 nm, new absorption maxima began to develop at ~325 and ~400 nm. On prolonged standing, the spectrum of the reaction mixture became identical with that of the dinitro carbanion **7**. The overall reaction appeared to involve a rapid conversion of 4,4,4-trinitrobutyronitrile to **9** followed by a slow transformation of **9** to **7**.

It was not possible to obtain good quality pseudo-first-order plots for the rate of formation of **9** by graphing log $([\mathbf{9}]_\infty - [\mathbf{9}]_t)$ *vs.* time, as the infinity value was not constant owing to the simultaneous conversion of **9** to **7**. However, if the specific rate of conversion of **9** to **7**, $k_N$ (Table V), is at least tenfold slower than its

TABLE V

REACTION OF $C(NO_2)_3CH_2CH_2CN$ WITH $OH^-$ IN THE PRESENCE OF $S_2O_3^{2-}$, 25°, $\mu$ = 0.1

| Run | [HA][a] | [A⁻] | $[S_2O_3^{2-}]$ | pH | $10^5[OH^-]$ | $k_2$, $M^{-1}$ sec$^{-1}$ | $10^4k_N$, sec$^{-1}$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.020 | 0.005 | 0.012 | 9.40 | 4.12 | 22.4 | 0.402 |
| 2 | 0.020 | 0.005 | 0.023 | 9.42 | 4.32 | 24.8 | 0.452 |
| 3 | 0.016 | 0.009 | 0.022 | 9.70 | 8.22 | 25.1 | 0.788 |
| 4 | 0.016 | 0.009 | 0.022 | 9.70 | 8.22 | 25.5 | 0.795 |
| 5 | 0.020 | 0.020 | 0.014 | 9.97 | 15.3 | 23.1 | 1.79 |
| 6 | 0.020 | 0.020 | 0.007 | 9.98 | 15.7 | 25.7 | 1.81 |
| 7 | 0.010 | 0.015 | 0.013 | 10.10 | 20.7 | 23.7 | 2.03 |
| 8 | 0.006 | 0.006 | 0.025 | 9.95 | 14.6 | 23.6 | 0.787 |
| 9 | 0.013 | 0.012 | 0.021 | 9.94 | 14.3 | 22.0 | 1.13 |
| 10 | 0.021 | 0.019 | 0.014 | 9.95 | 14.6 | 24.3 | 1.72 |
| 11 | 0.026 | 0.024 | 0.009 | 9.92 | 13.7 | 24.7 | 1.90 |

[a] $HCO_3^-/CO_3^{2-}$ buffers.

formation, $k_2[OH^-]$ (Table V), then a good approximation of $[\mathbf{9}]_\infty$ can be had by extrapolating the slope of the graph of log [**9**] *vs.* time for the conversion of **9** to **7** to zero time. In excess buffer, this reaction was found to be pseudo-first-order. A further complication arose from the fact that the product **7** has a molar extinction of 6400 at 368 nm, $\lambda_{max}$ for **9**.[22] Therefore, plots of log $OD_{368}$ *vs.* time will tend to develop upward curvature as the conversion of **9** to **7** progresses. Since it was not possible to isolate **9** so as to obtain an accurate value of its molar extinction for use in calculating the actual concentration of **9** in the **9** and **7** mixture, the initial slope of the log $OD_{368}$ *vs.* time plots was used for this extrapolation. Figure 1 presents the log $OD_{368}$ profile *vs.* time for a typical kinetic run together with the zero time extrapolation.

Using the extrapolated zero time value as $(OD_{368})_\infty$, $k_\psi$, the pseudo-first-order constant for the formation of **9**, was evaluated from the slope of the graph of log $[(OD_{368})_\infty - (OD_{368})_t]$ *vs.* time. These plots usually exhibited upward curvature about the beginning of the third half-life (Figure 1). This was expected, since the rate of conversion of **9** to **7** late in the reaction becomes appreciable and makes the observed $(OD_{368})_t$ less and hence $(OD_{368})_\infty - (OD_{368})_t$ greater than that calculated for a simple first-order rate of formation.

(22) For **9**, we estimate $\epsilon_{368} \sim 14{,}000$. This is based on the extrapolated value of $(O.D._{368})_\infty$ for the formation of **9** and the initial concentration of 4,4,4-trinitrobutyronitrile. Carbanions of the type $^-C(NO_2)_2CHOMeCH_2Y$, Y = $CO_2Me$, CN, and $SO_2Me$, have $\epsilon$ 14–16,000; unpublished results.

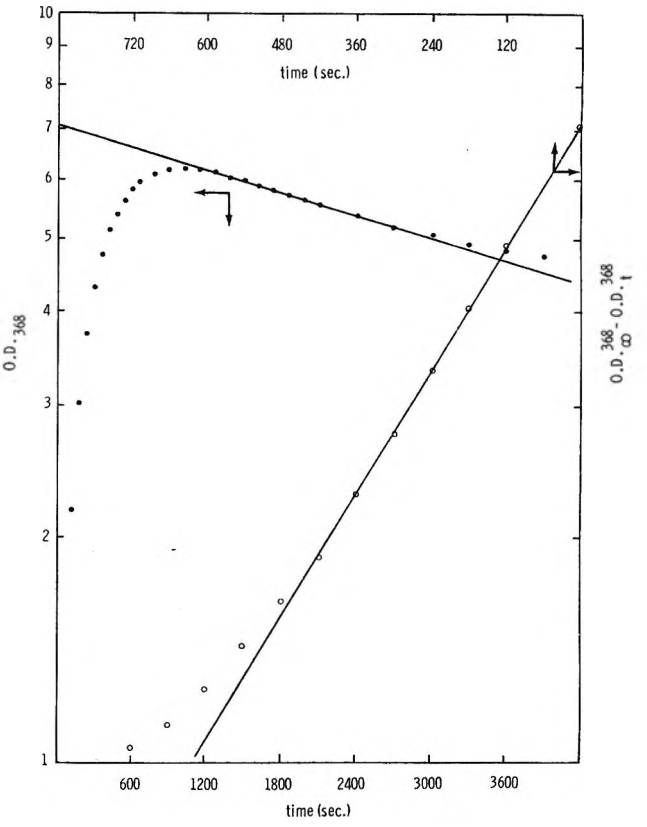



Figure 1.—Log $OD_{368}$ *vs.* time for the formation and disappearance of **9** (●); log $[(OD_{368})_\infty - (OD_{368})_t]$ *vs.* time for the formation of **9** (○). See run 9 in Table V for reagent concentrations.

Table V summarizes the values of $k_2$, $k_\psi/[OH^-]$, for the conversion of 4,4,4-trinitrobutyronitrile to **9**. The average value of $k_2$, 24.1 ± 1.0 $M^{-1}$ sec$^{-1}$, agrees exceptionally well with the value obtained in the absence of thiosulfate ion (Table IV). Therefore, in spite of the difference in the products formed in the presence and absence of thiosulfate ion, the formation of the olefin **6** is rate determining for both reactions.

The conversion of **9** to **7** is a rather interesting transformation. Over the pH range studied, **9** should be present as the dianion.[23] Inspection of the values of the pseudo-first-order constant $k_N$ in Table V shows a dependency of the specific rate on both the hydroxide, runs 1, 2, and 8, and buffer base, runs 8–11, concentrations but not on the thiosulfate concentration, runs 1, 2, 5, and 6. A mechanism in which proton abstraction from **9** is rate determining is consistent with these observations (eq 6 and 7). The conversion of the tri-

$$^-C(NO_2)_2CHCH_2CN + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^-C(NO_2)_2\bar{C}HCN + BH^+ \quad (6)$$

(**9** = $^-C(NO_2)_2CHCH_2CN$, $S_2O_3^-$; **10** = $^-C(NO_2)_2\bar{C}HCN$, $S_2O_3^-$)

$$^-C(NO_2)_2\bar{C}HCN \xrightarrow{k_2} {}^-C(NO_2)_2CH{=}CHCN + S_2O_3^- \quad (7)$$

(**10** → **7**)

anion **10** to **7** occurs rapidly, as thiosulfate ion is a good leaving group. The question of the magnitude of $k_{-1}$

(23) The p$K$'s of 1 1-dinitroalkanes are less than 6 [M. E. Sitzman, H. G. Adolph, and M. J. Kamlet, *J. Amer. Chem. Soc.*, **90**, 2815 (1968)] and the p$K$ of $HS_2O_3^-$ is ~2.[19]

[$BH^+$] relative to $k_3$ was answered by generating **9** in a buffered deuterium oxide–dioxane solvent system and allowing it to convert to **7** under these conditions. Since no deuterium uptake was observed at the $\alpha$ carbon atom of **7**, $k_3 \gg k_{-1}[BH^+]$ and the conversion of **9** to **7** occurs by a nonreversible carbanion mechanism.

Mechanisms involving a unimolecular displacement of thiosulfate ion from **9** (eq 8 and 9) can be ruled out

$$^-C(NO_2)_2CHCH_2CN \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C(NO_2)_2{=}CHCH_2CN + S_2O_3^{2-} \quad (8)$$
$$\quad S_2O_3^-$$
$$\quad 9 \qquad\qquad 6$$

$$C(NO_2)_2{=}CHCH_2CN + B \xrightarrow{k_3} {}^-C(NO_2)_2CH{=}CHCN + BH^+ \quad (9)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad 7$$

on the following grounds. If $k_{-1}[S_2O_3^{2-}] \gg k_3[B]$, then $k_N$ should decrease on increasing the thiosulfate ion concentration at constant pH and buffer base concentration. For the inverse, $k_{-1}[S_2O_3^{2-}] \ll k_3[B]$, **9** would not initially form from **6** and thiosulfate ion.

Mechanisms for the formation of the olefins **5** that are kinetically second order can be divided into two categories:[10] those requiring some degree of C–$NO_2$ bond breaking and double bond formation in the transition state (concerted E2) and those in which carbanion formation is rate determining. To distinguish between the two categories, we have applied the $\alpha$-fluorine effect[8,9] as a transition-state probe. As previously stated,[8,9] a process in which a ground-state carbon atom bearing a fluorine substituent gains s character on going to the transition state should be energetically disfavored relative to the nonfluorine-substituted carbon atom. Thus, for the substrates **4**, the ordering of $\Delta H^*$ values should be $NO_2 < Cl < F$ for a concerted process in which both C–$NO_2$ bond breaking and double bond formation make a contribution to the transition state.[24] The data in Table VI do not give rise to such an ordering. From this we conclude that neither C–$NO_2$ bond breaking nor double-bond formation has occurred to a significant extent in the transition state for the formation of **5**.

TABLE VI

ACTIVATION PARAMETERS FOR THE REACTION $ZC(NO_2)_2CH_2CH_2CN + OH^-$

| Z | $k_2$, $M^{-1}$ sec$^{-1}$ (25°) | $\Delta H^*$, kcal mol$^{-1}$ | $\Delta S^*$, cal deg$^{-1}$ |
|---|---|---|---|
| $NO_2$ | 15.9 ± 0.3[a] | 16.6 ± 0.4[a] | 2.5 ± 1.4[a] |
| F | 0.190 ± 0.004 | 17.1 ± 0.3 | −4.4 ± 1.1 |
| Cl | 0.114 ± 0.002 | 20.3 ± 0.2 | 5.1 ± 0.7 |

[a] Calculated from the statistically corrected values of $k_2$; Table IV, ref *f*.

Mechanisms of the second category are those in which carbanion formation precedes C–$NO_2$ bond breaking and double-bond formation. These are generalized by the following equations.

$$ZC(NO_2)_2CH_2CH_2CN + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ZC(NO_2)_2\bar{C}HCH_2CN + H_2O \quad (10)$$

$$ZC(NO_2)_2\bar{C}HCH_2CN \xrightarrow{k_2} ZC(NO_2){=}CHCH_2CN + NO_2^- \quad (11)$$

Two limiting conditions exist: (1) $k_3 \gg k_{-1}[H_2O]$, nonreversible carbanion elimination, and (2) $k_3 \ll k_{-1}[H_2O]$, reversible carbanion elimination. It was possible to distinguish between the two by carrying out the reaction in a buffered deuterium oxide–dioxane solvent system.[25] After approximately one-third of **4**, Z = $NO_2$, had been converted to **7**, neither the recovered **4** nor the olefin **7** were found to contain deuterium. Therefore, $k_3 \gg k_{-1}[H_2O]$ and every carbanion formed by $\beta$-proton abstraction loses nitrite to form the olefin **5** before it can be reprotonated to **4**.

The loss of the elements of nitrous acid from the substrates **4** by a nonreversible carbanion mechanism is reasonable in view of the structural factors present. Substituents such as $ZC(NO_2)_2$–, which have large $\sigma^*$ values,[12,13] enhance the acidity of the $\beta$ hydrogens, making them subject to facile removal by hydroxide. Stabilization of the resulting carbanion by the strong inductive effect slows down the rate of proton recombination. This rate retardation is coupled with the presence of a good leaving group, *i.e.*, nitro departing as resonance-stabilized nitrite ion. These factors combine to make $k_3 \gg k_{-1}[H_2O]$ (eq 10, 11).

The use of fluorine labeling appears to be a useful tool for distinguishing between a concerted elimination reaction and a second-order carbanion elimination reaction. We are attempting to apply this technique to other systems to determine both the mechanism of the reaction and the position of the transition state along the reaction coordinate.

## Experimental Section

*Caution! Many of the compounds described in this work will detonate on grinding or impact. Extreme care should be taken when handling dry salts of the nitrocarbanions.*

**4,4,4-Trinitrobutyronitrile** was prepared by adding 0.28 mol (15 g) of acrylonitrile to a solution of 0.265 mol (40 g) of trinitromethane in 125 ml of absolute ethanol. After standing for 24 hr at room temperature, the red-orange solution was poured into 500 ml of water and then extracted with three 100-ml portions of chloroform. The combined chloroform extracts were washed by percolating a stream of water through them until they were essentially colorless. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to about 100 ml. Pentane was added to the cloud point and the product crystallized on cooling in the freezer. It was rapidly filtered and dried with suction on the Buchner funnel. The solid melted at ambient temperature to an almost colorless liquid which was sufficiently pure for kinetic runs, as its nmr spectrum ($CHCl_3$–TMS) exhibited only a broad triplet, $\delta$ 3.47 (center), and a complex multiplet, $\delta$ 2.89 (center), of equal areas for the $\beta$-$CH_2$ and $\alpha$-$CH_2$, respectively, yield 38 g (70%).

**4,4-Dinitrobutyronitrile potassium salt** was prepared from the trinitromethyl derivative and methanolic potassium iodide.[26]

**4-Chloro-4,4-dinitrobutyronitrile** was obtained by suspending 0.05 mol (9.85 g) of the potassium salt of 4,4-dinitrobutyronitrile

(24) An estimate of the magnitude of the effect of an $\alpha$-fluorine substituent on $\Delta H^*$ is available from a similar effect on C$\beta$–H bond breaking in the elimination of hydrogen bromide from $\beta$-haloethyl bromides [J. Hine and P. B. Langford, *J. Amer. Chem. Soc.*, **78**, 5002 (1956)]. For this system, $\Delta H^*$ for fluorine is about 12 kcal mol$^{-1}$ larger than that for either chlorine or bromine.

(25) J. Hine, R. Wiesboeck, and O. B. Ramsay, *J. Amer. Chem. Soc.*, **83**, 1222 (1961); J. Hine, R. Wiesboeck, and R. G. Ghirardelli, *ibid.*, **83**, 1219 (1961); L. R. Fedor, *ibid.*, **91**, 908 (1969).

(26) D. J. Glover and M. J. Kamlet, *J. Org. Chem.*, **26**, 4734 (1961).

in 50 ml of methylene chloride and passing dry chlorine through the suspension until the yellow color was discharged. The precipitated potassium chloride was removed by filtration and washed with 50 ml of methylene chloride, and the combined extracts were washed with 50 ml of saturated sodium bicarbonate (to remove dinitrobutyronitrile) and 100 ml of water and dried over magnesium sulfate. After the organic phase was treated with Darco G-60 charcoal, the solvent was removed *in vacuo*. The residual oil was flash distilled at 90° (0.1 mm) to yield 7.5 g (78%) of a pale yellow oil. *Anal.* Calcd for $C_4H_4ClN_3O_4$: C, 24.8; H, 2.1; N, 21.7; Cl, 18.3. Found: C, 24.9, 24.8; H, 2.0, 2.0; N, 20.3, 20.4; Cl, 18.2, 18.2.

**4,4-Dinitro-4-fluorobutyronitrile** was prepared by fluorinating a solution of 0.026 mol (5 g) of the potassium salt of 4,4-dinitrobutyronitrile in 200 ml of water containing 2.5 g of sodium bicarbonate with a stream of fluorine–nitrogen (1:3) until the yellow color of the solution was discharged. The turbid mixture was extracted with three 50-ml portions of methylene chloride. The combined extracts were washed with 5% sodium bicarbonate and then water and dried over magnesium sulfate. After the solvent was removed *in vacuo*, the residual oil was distilled at 70° (0.3 mm) to yield 3.6 g (78%) of a colorless oil. *Anal.* Calcd for $C_4H_4FN_3O_4$: C, 27.1; H, 2.3; N, 23.7; mol wt, 177. Found: C, 27.1, 27.5; H, 2.4, 2.5; N, 22.9, 22.3; mol wt, 174, 178 (osmometer).

**4-Chloro-4,4-dinitrobutyric acid and 4,4-dinitro-4-fluorobutyric acid** were prepared as described previously.[12]

**4-Fluoro-4-nitro-2-butenoic acid dipotassium salt** was prepared by adding a solution of 0.02 mol (3.92 g) of 4,4-dinitro-4-fluorobutyric acid in 20 ml of methanol to a solution of 0.1 mol (5.6 g) of potassium hydroxide in 50 ml of methanol. After 1 hr, the salt was collected by filtration, washed twice with 10-ml portions of methanol and once with 10 ml of ether, and air dried. The pink salt, 2.66 g (60%), could not be recrystallized without extensive decomposition and was therefore analyzed directly. *Anal.* Calcd for $K_2C_4H_2FNO_4$: K, 34.7; C, 21.3; H, 0.89; N, 6.2. Found: K, 33.8; C, 21.4; H, 1.1; N, 6.6.

**4-Chloro-4-nitro-2-butenoic acid dipotassium salt** was prepared by adding a solution of 0.01 mol (2.12 g) of 4-chloro-4,4-dinitrobutyric acid in 10 ml of ether to a solution of 0.05 mol (2.8 g) of potassium hydroxide in 20 ml of methanol. There was an almost immediate precipitation of an amorphous orange salt. The product could not be recrystallized, and, after it was washed with 50% ether in methanol, its ultraviolet spectrum, $\lambda_{max}$ 322 nm ($\epsilon$ 12,400), indicated that the salt was not pure, as the value of the molar extinction coefficient seemed low. However, no impurities were detected in its nmr spectrum (Table III). Therefore, the contaminants were assumed to be inorganic.

The proof of a single reaction path and a good value of the molar extinction coefficient were obtained by the following procedure in which a mole for mole correspondence between the nitrite ion and 4-chloro-4,4-dinitrobutyric acid concentrations were obtained. A sample of $1.006 \times 10^{-4}$ mol (0.021384 g) of 4-chloro-4,4-dinitrobutyric acid was rinsed into a 100-ml volumetric flask with 5 ml of methanol and 25 ml of water added. Then 5 ml of 20 *M* sodium hydroxide was introduced, and the solution was mixed thoroughly and allowed to stand for 30 min. After it was diluted to volume with water, a 6-ml aliquot was diluted to 100 ml with water. The ultraviolet spectrum of this solution exhibited $\lambda_{max}$ 322 nm ($\epsilon$ 16,400), $OD_{322}$ = 0.990. Analysis of this dilution for nitrite[14] gave $10^5[NO_2^-]$ = 6.01. For a quantitative conversion of the 4-chloro-4,4-dinitrobutyric acid originally present in this dilution $10^5[NO_2^-]$ = 6.04. No chloride ion could be detected in this reaction mixture.

**4-Chloro- and 4-Fluoro-4-nitro-2-butenenitrile Potassium Salt.**—On a synthetic scale, it was not possible to isolate these products, as they were apparently unstable out of solution. Molar extinction coefficients and proof of a single reaction path for their formation were determined in the following manner. A solution of $1.26 \times 10^{-4}$ mol (0.024613 g) of 4-chloro-4,4-dinitrobutyronitrile in 5 ml of methanol in a 100-ml volumetric flask was diluted to volume with 0.1 *M* sodium hydroxide. Samples were withdrawn at intervals and appropriately diluted with water, and the absorbance was measured at 342 nm. After about 45 min, the value of the absorbance was constant and 6 ml of the reaction mixture was diluted to 100 ml with water. The spectrum of this dilution showed $\lambda_{max}$ 342 mm ($\epsilon$ 13,800), OD = 1.043. Nitrite ion was equal to $7.74 \times 10^{-5}$ *M* as compared with $7.56 \times 10^{-5}$ *M* 4-chloro-4,4-dinitrobutyronitrile originally present in this dilution.

For 4,4-dinitro-4-fluorobutyronitrile, using 0.2 *M* sodium hydroxide as the reaction medium, $10^5[FC(NO_2)_2CH_2CH_2CN]$ = 4.00, $10^5[NO_2^-]$ = 4.12, $\lambda_{max}$ 335 nm ($\epsilon$ 23,000), OD = 0.920.

**Reaction of 4,4,4-Trinitrobutyronitrile with Hydroxide in Dioxane–$D_2O$.**—To a solution of 0.05 mol (5 g) of potassium bicarbonate in 70 ml of $D_2O$ and 55 ml of purified dioxane[14] was added 0.01 mol (2.04 g) of 4,4,4-trinitrobutyronitrile. The course of the reaction was followed spectrophotometrically and after 35 min, 36% of the trinitro species had reacted. The mixture was extracted with four 20-ml portions of methylene chloride. The combined extracts were washed with 20 ml of $D_2O$ and dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residual oil was analyzed for deuterium by comparing the integral at $\delta$ 3.47 for $\beta$-$CH_2$ (29.8 ± 0.7) with the integral at $\delta$ 2.89 for $\alpha$-$CH_2$ (29.5 ± 0.3) in the recovered starting material.

The elimination product **7** was isolated by concentrating the aqueous phase under reduced pressure (60°) till the orange potassium salt separated from solution. The product was collected on a Buchner, washed with methanol and then ether, and dried. The integrals of the two doublets for the olefinic protons at $\delta_{H_\beta}$ 7.75 and 7.91 and $\delta_{H_\alpha}$ 5.86 and 6.02 (DMSO–TMS) were 61.0 ± 0.0 and 61.0 ± 0.7. Therefore, no deuterium was picked up from the solvent during the reaction.

**Reaction of 4,4,4-Trinitrobutyronitrile with Hydroxide and Thiosulfate in Dioxane–$D_2O$.**—The procedure described above was followed except that 0.05 mol (12.4 g) of sodium thiosulfate pentahydrate was dissolved in the reaction medium prior to the addition of the trinitro substrate. The course of the reaction was followed spectrophotometrically on diluted aliquots and after 3 hr at 50° essentially all of the first formed thiosulfate ester **9**, $\lambda_{max}$ 368 nm, was converted to the olefin **9**. The reaction mixture was concentrated *in vacuo* (60°) till crystallization just started. After cooling in ice water, the salt was collected on a Buchner funnel, washed with methanol and then ether, and dried. Integrals of the two doublets for the olefinic protons in the nmr spectrum of **7** (DMSO–TMS) were equal to 68.3 ± 0.3 and 69.0 ± 0.7 for $CH_\beta$ and $CH_\alpha$, respectively.

**General Kinetic Procedure.**—Appropriate aliquots of stock solutions of the buffer components, added salt, and when necessary sodium thiosulfate were added to a 100-ml volumetric flask. Distilled water was added to a volume of about 90 ml and the resulting solution was thermostated at the desired temperature for 30 min. To this solution was added an aliquot (5 ml or smaller) of the thermostated nitro substrate stock solution (about $1–5 \times 10^{-3}$ *M*) in 5% aqueous methanol. The mixture was made up to volume with thermostated distilled water and mixed by shaking, and a sample was transferred to a thermostated cell in a Cary Model 14 spectrophotometer. This procedure generally took about 1 min. The increase in absorbance at $\lambda_{max}$ for the product (Table II) was followed with time. The pH measurements were made on a thermostated sample of the reaction mixture with either a Beckman Model G or Research pH meter. Rate constants were calculated from these data as described in the Results and Discussion section.

**Registry No.**—$C(NO_2)_3CH_2CH_2CN$, 15473-29-7; $FC(NO_2)_2CH_2CH_2CN$, 21823-64-3; $ClC(NO_2)_2CH_2$-$CH_2CN$, 22917-74-4; 4-fluoro-4-nitro-2-butenoic acid dipotassium salt, 36529-41-6; 4-chloro-4-nitro-2-butenoic acid dipotassium salt, 36529-42-7.

**Acknowledgment.**—This work was supported by the Independent Research Fund of the U. S. Naval Ordnance Laboratory, Task IR-044.

# Decarboxylation of 5-Substituted 2-Pyridinecarboxylic Acids[1]

RUSSELL J. MOSER AND ELLIS V. BROWN*[2]

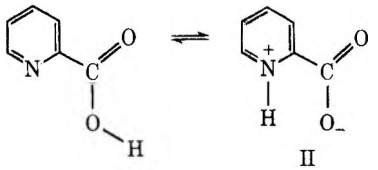
*Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506*

*Received February 19, 1971*

The rates of decarboxylation of 5-nitro-2-pyridinecarboxylic, 2,5-pyridinedicarboxylic, 5-iodo-2-pyridinecarboxylic, and 5-methoxy-2-pyridinecarboxylic acids in 3-nitrotoluene have been measured. The $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were then calculated. An examination of the linear free-energy plot of relative rates *vs.* the $\sigma_p$ constants suggests that electron withdrawal from the 5 position results in lower $\Delta G^{\ddagger}$ values. The observation that 2-pyridinecarboxylic acid does not fall on the same straight line as these acids, suggests that I can either lead to the cyclic transition state (IV) or to the zwitterion intermediate (II) which then decarboxylates. The pathway that a particularly substituted 2-pyridinecarboxylic acid follows depends upon the electron density on the ring nitrogen. A mechanism is given which is consistent with the available data. An assumption of this interpretation is that some monomer exists in solution at high temperature.

The decarboxylation of 2-pyridinecarboxylic acid in various solvents,[3-5] of methyl-substituted 2-pyridinecarboxylic acids,[6] and of 6-substituted 2-pyridinecarboxylic acids[7] has been studied in two different laboratories. Earlier investigators[3-6] found no correlation between the rates of decarboxylation and structure of the transition state. They did try to deduce the structure of the intermediate leading to the transition state. Different methods should be used to study the distribution of reactants other than those used to deduce the structure of the transition state. Thus, we have not postulated that either I or II is the principal reactant, but assumed that both are present and a rapid equilibrium exists between them (Scheme I). We

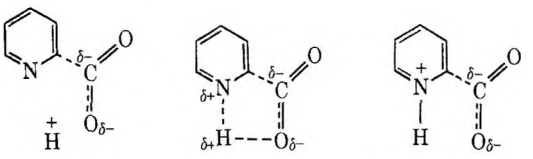
SCHEME I



I II

have also assumed that some monomer is present in solution at the temperatures used in this study. The assumption that some monomer is present at these temperatures,[8] in this solvent,[9] and at the concentrations[10] used in this study is a reasonable one based on evidence with other acids.

Irrespective of which reactant leads to which transition state, there are three reasonable transition states III, IV, and V which could yield apparent first-order kinetics. The electrical effects in these three transition states are different. If transition states III or V lead predominantly to decarboxylation, electron-withdrawing substituents would stabilize the transition



III IV V

state and lead to larger rate constants. If transition state IV leads to products, there are opposing effects. At one position, electron withdrawal would increase the rate constants and, at the other position, decrease the rate constants. Two events are occurring in transition state IV: (a) N–H bond formation and (b) C–C bond cleavage. With these two events, there are three pathways for the reaction to take place: (a) C–C bond cleavage is leading N–H bond formation, resulting in a developing negative charge on C-2 in the transition state, (b) C–C bond cleavage is lagging behind N–H bond formation resulting in a developing positive charge on the ring nitrogen in the transition state, or (c) C–C bond cleavage has progressed at an even rate with N–H bond formation, resulting in no overall charge being developed on the ring in the transition state.

If the electron density on the ring nitrogen is changed (without changing anything else) by substituents, a rate change should be seen if N–H bond formation is leading C–C bond cleavage in the transition state. The electron density on the ring nitrogen is influenced by inductive effects[7,11,12] (*i.e.*, $\sigma_m$ or $\sigma'$). If the electron density on the 2 carbon is changed (without changing anything else) by substituents, the rate constants should change if C–C bond cleavage leads N–H bond formation in the transition state. It has been shown that substituents para to the 2 position do affect the electron density at the 2 position. This relationship correlates well with $\sigma_p$.[13] Thus it should be possible to tell whether N–H bond formation or C–C bond cleavage is the major reaction in the transition state by observing if a linear relationship exists with $\sigma_m$, $\sigma'$, or $\sigma_p$ *vs.* log $k/k_0$. If pathway a exists, this method will not eliminate any of the possible transition states without reasonable assumptions, and, if pathway c exists, then the method will not work. It has been shown that transition state IV (pathway b) is used by the 6-substituted 2-pyridinecarboxylic acids by the ob-

(1) Presented in part at the Combined 22nd Southeastern and 26th Southwestern Regional Meetings of the American Chemical Society, New Orleans, La., Dec 1970.

(2) To whom inquiries should be made.

(3) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).

(4) L. W. Clark, *ibid.*, **69**, 2277 (1965).

(5) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **74**, 5967 (1952).

(6) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953).

(7) R. J. Moser and E. V. Brown, *J. Org. Chem.*, **36**, 454 (1971).

(8) See, for example, H. E. Hallam in "Infrared Spectroscopy and Molecular Structure," M. Davies, Ed., Elsevier, New York, N. Y., 1963, Chapter XII.

(9) See, for example, B. Harrow, and A. Mazer, "Textbook of Biochemistry," 9th ed, W. B. Saunders Co., Philadelphia, Pa., 1968, p 63.

(10) C. M. Huggins, G. C. Pimentel, and J. N. Shoolery, *J. Phys. Chem.*, **60**, 1311 (1956).

(11) H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.*, **77**, 4444 (1955).

(12) M. Charton, *ibid.*, **86**, 2033 (1964).

(13) Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1293 (1959); *Chem. Abstr.*, **55**, 6476c (1960).

servation that electron-withdrawing substituents at the 6 position increase $\Delta G^{\ddagger}$ values.[7] In this case there was a linear relationship between $\sigma'$ *vs.* ln $k_1/k_0$ (see Figure 1).

## Results and Discussion

The 5-substituted 2-pyridinecarboxylic acids, 5-nitro-2-pyridinecarboxylic, 2,5-pyridinedicarboxylic, 5-iodo-2-pyridinecarboxylic, and 5-methoxy-2-pyridinecarboxylic acids were synthesized and their rates of decarboxylation in 3-nitrotoluene were determined. The rate constants are in Table I, and the activation parameters are in Table II. The coefficient of variation for the data has been calculated in each case. This value is used as a measure of the relative variability of the data. In all cases it is <5%. To get an assurance that the carboxyl group at the 5 position in 2,5-pyridinedicarboxylic acid was not removed under the conditions employed, the rate of decarboxylation of 3-pyridinecarboxylic, 2-chloro-5-pyridinecarboxylic, and 2-nitro-5-pyridinecarboxylic acids at temperatures up to 200° were studied. No carbon dioxide was evolved. This has been noted previously.[14]

Table I

Apparent First-Order Rate Constants for the Decarboxylation of 5-Substituted 2-Pyridinecarboxylic Acids in 3-Nitrotoluene

| Acid (registry no.) | Temp, °C | Rate constant[a] × $10^a$ $sec^{-1}$ | Coefficient variation[b] |
|---|---|---|---|
| 5-Nitro-2-pyridine-carboxylic acid (30651-24-2) | 156.6 | 1.34 | 0.94 |
| | 159.8 | 1.78 | 0.90 |
| | 166.2 | 3.39 | 0.50 |
| | 170.5 | 4.63 | 1.57 |
| | 174.5 | 6.65 | 0.57 |
| | 180.0 | 10.65[c] | |
| 2,5-Pyridinedicarboxylic acid (100-26-5) | 166.0 | 2.03 | 1.01 |
| | 170.4 | 3.30 | 1.38 |
| | 175.2 | 3.86 | 2.44 |
| | 180.0 | 5.91[c] | |
| | 180.5 | 6.50 | 1.84 |
| | 184.4 | 7.78 | 2.73 |
| 5-Iodo-2-pyridine-carboxylic acid (32046-43-8) | 170.0 | 0.97 | 0.63 |
| | 175.8 | 1.83 | 0.46 |
| | 180.0 | 2.60[c] | |
| | 180.1 | 2.63 | 0.54 |
| | 185.7 | 4.33 | 0.89 |
| | 190.0 | 6.39 | 1.29 |
| 2-Pyridinecarboxylic acid[d] (98-98-6) | 158.5 | 0.57 | 3.51 |
| | 163.6 | 1.22 | 4.31 |
| | 169.8 | 1.92 | 1.21 |
| | 175.5 | 2.96 | 1.73 |
| | 179.5 | 4.49 | 1.14 |
| 5-Methoxy-2-pyridine-carboxylic acid (29082-92-6) | 180.0 | 0.36[c] | |
| | 189.6 | 0.95 | 0.39 |
| | 194.9 | 1.58 | 0.24 |
| | 200.2 | 2.89 | 1.05 |
| | 204.2 | 3.95 | 0.76 |
| | 210.0 | 6.78 | 1.43 |

[a] The initial concentration is $\sim 10^{-2}$ *M* in acid. [b] The coefficient of variation is calculated as follows: [(standard deviation) ÷ (average value of ln $a/a - x$)] × 100. [c] Calculated from rate constants at other temperatures. [d] See ref 7.

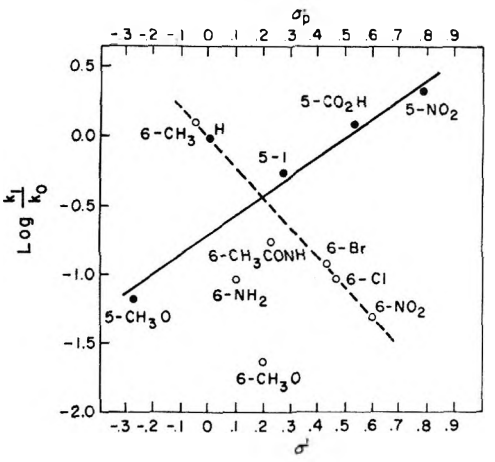



Figure 1.—A plot of $\sigma$ *vs* log $k_1/k_0$. The 6 substituents (from ref 7) are plotted $\sigma'$ *vs.* log $k_1/k_0$ at 200° and the 5 substituents are plotted $\sigma_p$ *vs.* log $k_1/k_0$ at 180°.

Table II shows that, as the electron-withdrawing ability of substituents increase, the activation energies ($\Delta G^{\ddagger}$) decrease. 2-Pyridinecarboxylic acid does not fit into this generalization, and it will be discussed later. A correlation of rates of decarboxylation *vs.* $\sigma_m$ or $\sigma'$ was not found. Figure 1 shows that a linear relationship exists between the $\sigma_p$ values of the 5-nitro, 5-carboxyl, 5-iodo, and 5-methoxyl groups and their relative rate constants. The slope of this line is +1.4. A positive value of this magnitude indicates that a negative charge is being developed in the transition state. This does not eliminate any of the proposed transition states, since a negative charge can be developed in any of them. Transition state III can be eliminated because it is difficult to envision a decarboxylation mechanism under the present conditions that does not involve acid–base interaction as in transition state IV and V. Because different trends were observed in the Hammett $\sigma\rho$ plots the transition state for the 5-substituted 2-pyridinecarboxylic acids must be different from the transition state for the 6-substituted 2-pyridinecarboxylic acids (see Figure 1). The first approach to present a unifying picture of decarboxylation of 5- and 6-substituted acids is to assume that, if IV is the transition state for both the 5- and 6-substituted 2-pyridinecarboxylic acids, then pathway a and not b exists in this case. This results in a developing negative charge at C-2 in the transition state. This idea is dismissed because it is difficult to explain why N–H bond formation should lead C–C bond cleavage in the 6-substituted 2-pyridinecarboxylic acids and not in the 5-substituted 2-pyridinecarboxylic acids. The electron density on the ring nitrogen is less affected by a 5 substituent than a 6 substituent. This type of argument eliminates transition state IV.

A more satisfying mechanism is presented in Scheme II. Assume that the two steps in transition state IV, bond making and bond breaking, are affected by substituents. N–H bond formation is difficult in the 6-substituted 2-pyridinecarboxylic acids, because electron withdrawal by the inductive effect from the nitrogen would be strong. These acids decarboxylate by transition state IV in the top mechanism (*i.e.*, N–H bond formation is the determining factor). N–H bond formation is easier in the 5-substituted 2-pyridinecarboxylic acids, because of the meta position and greater

(14) A. Kaneda and T. Hara, *Sci. Eng. Rev. Doshisha Univ.*, **7**, 172 (1967).

TABLE II

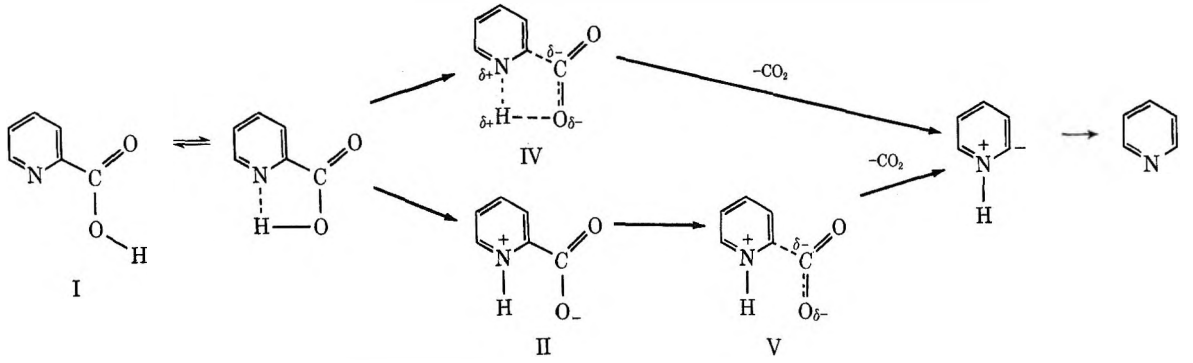
APPARENT FIRST-ORDER ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF 5-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

| Acid | $\Delta G^{\ddagger}_{180}$, kcal/mol | $E_{act}$, kcal/mol | $\Delta H^{\ddagger}_{180}$, kcal/mol | $\Delta S^{\ddagger}_{180}$, cal/deg mol | Coefficient variation[a] |
|---|---|---|---|---|---|
| 5-Nitro-2-pyridinecarboxylic acid | 33.06 | 34.19 | 33.25 | +0.40 | 0.34 |
| 2,5-Pyridinedicarboxylic acid | 33.86 | 28.66 | 27.72 | −12.97 | 1.03 |
| 5-Iodo-2-pyridinecarboxylic acid | 34.21 | 38.13 | 37.19 | +6.28 | 0.39 |
| 2-Pyridinecarboxylic acid[b] | 33.71 | 36.54 | 35.60 | +3.99 | 1.14 |
| 5-Methoxy-2-pyridinecarboxylic acid | 35.87 | 42.98 | 42.04 | +13.04 | 0.41 |

[a] This is the value for the least-square fit in the calculation of $E_{act}$. It is calculated as follows: [(standard deviation) ÷ (average value of ln $k$)] × 100. [b] See ref 7.

SCHEME II

SUGGESTED MECHANISMS FOR DECARBOXYLATION OF 2-PYRIDINECARBOXYLIC ACID




distance of the substituent from the ring nitrogen. These acids decarboxylate by transition state V in the bottom mechanism (*i.e.*, C–C bond cleavage is the determining factor).

One of the results of a Hammett $\sigma\rho$ plot is that all of the compounds which fall on the plotted line decarboxylate by the same mechanism if the $\Delta S^{\ddagger}$ is relatively constant or increases[15] with increasing $\Delta H^{\ddagger}$. We propose that 5-nitro-, 5-carboxy-, 5-iodo-, and 5-methoxy-2-pyridinecarboxylic acids all have transition state V for decarboxylation, and it is shown in the bottom mechanism of Scheme II.

2-Pyridinecarboxylic acid does not fall on the line in Figure 1 for the 5-substituted 2-pyridinecarboxylic acids. This points out the fact that two different mechanisms do operate in the decarboxylation of the 5- and 6-substituted 2-pyridinecarboxylic acids. This acid does fall on the Hammett plot for the 6-substituted 2-pyridinecarboxylic acids. Thus, 2-pyridinecarboxylic acid has a transition state in which N–H bond formation leads C–C bond cleavage. This acid decarboxylates by the top mechanism in Scheme II. Why 2-pyridinecarboxylic acid should decarboxylate like the 6-substituted acids and not the 5-substituted acids is open to speculation.

(15) H. H. Jaffé and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).

## Experimental Section

The apparatus and procedure used to collect the kinetic data has been described previously.[7] All of the acids had satisfactory C, H, and N analyses which are reported only for new compounds. Melting points were determined with a Fisher-Johns block and are uncorrected.

**Preparation of 5-Nitro-2-pyridinecarboxylic Acid.**—6-Chloro-5-nitro-2-methylpyridine was prepared as described.[16] This compound was then reduced to 5-nitro-2-methylpyridine[17] and oxidized to the corresponding acid.[17] It had mp 209° (lit.[18] mp 210°).

**Preparation of 2,5-Pyridinedicarboxylic Acid.**—This compound was purchased from Aldrich Chemical Co., Inc. It had mp 257° (lit.[18] mp 256–285°).

**Preparation of 5-Iodo-2-pyridinecarboxylic Acid.**—The method of Plazek and Rodewald was used to prepare 5-iodo-2-methylpyridine.[19] This compound was then oxidized to 5-iodo-2-pyridinecarboxylic acid.[20] It had mp 202° (lit.[18] mp 204°).

**Preparation of 5-Methoxy-2-pyridinecarboxylic Acid.**—This compound was prepared by M. B. Shambhu. 5-Methoxy-2-methylpyridine was prepared[21] then oxidized to the acid.[17]

*Anal.* Calcd for $C_7H_7O_3N$: C, 54.8; H, 4.6; N, 9.2. Found: C, 54.5; H, 4.9; N, 9.1.

(16) H. E. Baumgarten and H. C. Su, *J. Amer. Chem. Soc.*, **74**, 3828 (1952).

(17) E. V. Brown, *ibid.*, **76**, 1367 (1954).

(18) E. P. Oliveto, *Heterocycl. Compounds*, **14** (3), Chapter 10 (1962).

(19) E. Plazek and Z. Rodewald, *Rocz. Chem.*, **21**, 150 (1947); *Chem. Abstr.* **42**, 5456*b* (1948).

(20) G. Gerrari and E. Marcon, *Educ. Sci.*, **14**, 594 (1959); *Chem. Abstr.*, **54**, 6709*a* (1960).

(21) L. Marion and W. F. Cockburn, *J. Amer. Chem. Soc.*, **71**, 3403 (1949).

# Notes

## Decarboxylation of Some 2-Substituted Pyridinecarboxylic Acids

Russell J. Moser and Ellis V. Brown*

*Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506*

*Received September 3, 1970*

Previous investigations have dealt with the decarboxylation of 2-pyridinecarboxylic acids in various solvents.[1-6]

We believed that 3- and 4-pyridinecarboxylic acids would not decarboxylate in 3-nitrotoluene at measureable rates since the rates of decarboxylation of these acids (266°, $k = 6.0 \times 10^{-5}$ sec$^{-1}$, and 288°, $k = 6.0 \times 10^{-5}$ sec$^{-1}$, respectively) in pyrene are so small.[7] We felt that by placing electron-withdrawing and -attracting groups at the 2 position we might be able to lower the temperature at which decarboxylation takes place.

We synthesized 2-chloro- and 2-nitro-$x$-pyridinecarboxylic acids ($x$ = 3, 4, and 5) and 2-bromo-, 2-amino-, and 2-acetamido-3-pyridinecarboxylic acids and determined their rates of decarboxylation in 3-nitrotoluene. We then compared them with the rate of decarboxylation of 3-pyridinecarboxylic acid in 3-nitrotoluene. The rate constants are summarized in Table I. All of the rates reported have been duplicated. We wish to point out that the coefficients of variation are not so small as usually expected. The rates at the lowest temperature are at the lower limit for convenient measurement with our apparatus. This and the boiling point of 3-nitrotoluene (232°) contributed to the difficulty. However, we feel that the significant point is that at all temperatures used the relative order of the rates of decarboxylation was the same.

**2-Substituted 3-Pyridinecarboxylic Acids.**—2-Nitro-, 2-chloro-, and 2-bromo-3-pyridinecarboxylic acids decarboxylated below 227° in 3-nitrotoluene. We attempted to decarboxylate 3-pyridinecarboxylic acid in 3-nitrotoluene at 202 and 222°, but in neither case did the acid decarboxylate at a measureable rate. Some carbon dioxide did evolve at both temperatures; however, no accurate determination of a rate constant was possible. We found that the rate of decarboxylation decreased as the electron-withdrawing ability of the substituent decreased; consequently, electron-donating substituents should not encourage decarboxylation at these temperatures. This was found to be the case for a mixture of 2-amino-3-pyridinecarboxylic acid and 2-acetamido-3-pyridinecarboxylic acid.

Table I

Rate Data for the Decarboxylation of 2-Substituted Pyridinecarboxylic Acids in 3-Nitrotoluene

| Compd (registry no.) | Temp, °C | Rate constant $\times 10^4$ sec$^{-1}$ | Coefficient variation |
|---|---|---|---|
| 2-Nitro-3-pyridine-carboxylic acid (33225-72-8) | 211 | 1.2 | 4.3 |
| | 216 | 2.0 | 2.1 |
| | 221 | 3.8 | 6.8 |
| | 227 | 6.5 | 5.3 |
| 2-Nitro-4-pyridine-carboxylic acid (33225-74-0) | 217.2 | N.R.[a] | |
| 2-Nitro-5-pyridine-carboxylic acid (33225-73-9) | 193.5 | N.R. | |
| | 216.0 | N.R. | |
| 2-Nitro-6-pyridine-carboxylic acid[b] (26893-68-5) | 189.9 | 0.53 | 3.76 |
| | 195.0 | 0.78 | 1.26 |
| | 199.7 | 1.47 | 1.82 |
| | 204.8 | 2.16 | 4.10 |
| | 210.1 | 2.99 | 2.02 |
| 2-Chloro-3-pyridine-carboxylic acid (2942-59-8) | 209 | 0.7 | 1.4 |
| | 215 | 1.0 | 1 |
| | 219 | 1.3 | 8 |
| | 227 | 1.7 | 1.4 |
| 2-Chloro-4-pyridine-carboxylic acid (6313-54-8) | 225.0 | <0.1 | |
| 2-Chloro-5-pyridine-carboxylic acid (5326-23-8) | 224.4 | ≤0.1 | |
| 2-Chloro-6-pyridine-carboxylic acid[b] (4684-94-0) | 190.3 | 0.93 | 0.70 |
| | 194.6 | 1.74 | 2.24 |
| | 200.4 | 2.12 | 4.04 |
| | 205.3 | 3.71 | 1.08 |
| | 210.9 | 6.39 | 2.17 |
| 2-Bromo-3-pyridine-carboxylic acid (35905-85-2) | 210 | 0.58 | 9.2 |
| | 215 | 0.74 | 8.7 |
| | 220 | 0.91 | 9.2 |
| | 223 | 1.1 | 8.9 |
| 3-Pyridinecarboxylic acid (59-67-6) | 202 | <0.1 | |
| | 222 | ≤0.1 | |
| Mixture of 2-amino-3-pyridinecar-boxylic acid and 2-acetamido-3-pyridinecarboxylic acid | 220.8 | N.R. | |

[a] No reaction. [b] R. J. Moser and E. V. Brown, *J. Org. Chem.*, **36**, 454 (1971).

**Other 2-Substituted Pyridinecarboxylic Acids.**—After observing that electron-withdrawing groups at the 2 position lower the activation energy of decarboxylation for the 3-pyridinecarboxylic acids, we decided to investigate if this electron-withdrawing effect would lower the temperature of decarboxylation of the other 2-substituted pyridinecarboxylic acids. We synthesized 2-nitro- and 2-chloro-$x$-pyridinecarboxylic acids ($x$ = 4 and 5) and attempted to decarboxylate them. None of these acids decarboxylated in

(1) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).
(2) L. W. Clark, *ibid.*, **69**, 2277 (1965).
(3) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **74**, 5967 (1952).
(4) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953).
(5) R. J. Moser and E. V. Brown, *J. Org. Chem.*, **36**, 454 (1971).
(6) A. Kandea and T. Hara, *Sci. Eng. Rev. Doshisha Univ.*, **7**, (4), 172 (1967).
(7) H. Schenkel and M. Schenkel-Klein, *Helv. Chim. Acta*, **31**, 924 (1948).

3-nitrotoluene at measurable rates below 227°. Thus, it seems clear that electron-withdrawing substituents at the 2 position will significantly increase the rate of decarboxylation of 3-pyridinecarboxylic acid only.

### Experimental Section

Starting material, unless otherwise specified, is 2-amino-$x$-methylpyridine ($x$ = 3, 4, and 5) purchased from Reilly Tar and Chemical Corp., Chicago, Ill. The apparatus and procedure used to collect the kinetic data has been described previously.[5] Melting points were determined with a Fisher-Johns block and are uncorrected.

**Preparation of 2-Nitro-3-pyridinecarboxylic Acid.**—This compound was prepared *via* oxidation of the amino group[8] followed by oxidation of the methyl group[9] of 2-amino-3-methylpyridine. It had mp 156° (lit.[10] mp 156°).

*Anal.* Calcd for $C_6H_4N_2O_4$: C, 42.8; H, 2.4; N, 16.7. Found: C, 42.7; H, 2.9; N, 16.4.

**Preparation of 2-Nitro-4-pyridinecarboxylic Acid.**—2-Nitro-4-pyridinecarboxylic acid was synthesized from 2-amino-4-methylpyridine by the same procedure as above. It had mp 174° (lit.[10] mp 175°).

*Anal.* Calcd for $C_6H_4N_2O_4$: C, 42.8; H, 2.4; N, 16.7. Found: C, 42.7; H, 2.3; N, 16.4.

**Preparation of 2-Nitro-5-pyridinecarboxylic Acid.**—This compound was prepared from 2-amino-5-methylpyridine by the same procedure as used to make 2-nitro-3-pyridinecarboxylic acid. It had mp 183° (lit.[10] mp 183°).

*Anal.* Calcd for $C_6H_4N_2O_4$: C, 42.8; H, 2.4; N, 16.7. Found: C, 42.4; H, 2.5; N, 16.3.

**Preparation of 2-Chloro-3-pyridinecarboxylic Acid.**—2-Chloro-3-pyridinecarboxylic acid was synthesized *via* diazotization of the amino group[11] followed by oxidation of the methyl group[9] of 2-amino-3-methylpyridine. It had mp 200–201° (lit.[10] mp ~192–193°).

*Anal.* Calcd for $C_6H_4ClNO_2$: C, 45.7; H, 2.5; N, 8.9. Found: C, 45.4; H, 2.8; N, 9.2.

**Preparation of 2-Chloro-4-pyridinecarboxylic Acid.**—This compound was prepared from 2-amino-4-methylpyridine by the same procedure as above. It had mp 249–251° (lit.[10] mp 245°).

*Anal.* Calcd for $C_6H_4ClNO_2$: C, 45.7; H, 2.5; N, 8.9. Found: C, 45.4; H, 2.8; N, 9.2.

**Preparation of 2-Chloro-5-pyridinecarboxylic Acid.**—2-Amino-5-methylpyridine was diazotized and oxidized to prepare 2-chloro-5-pyridinecarboxylic acid by the same procedure as used to make 2-chloro-3-pyridinecarboxylic acid. It had mp 194–195° (lit.[10] mp ~199°).

*Anal.* Calcd for $C_6H_4ClNO_2$: C, 45.7, H, 2.5; N, 8.9. Found: C, 45.9; H, 2.8; N, 9.0.

**Preparation of 2-Bromo-3-pyridinecarboxylic Acid.**—2-Bromo-3-pyridinecarboxylic acid was synthesized *via* diazotization[12] followed by oxidation[9] of 2-amino-3-methylpyridine. It had mp 254° (lit.[10] mp 249–250°).

*Anal.* Calcd for $C_6H_4BrNO_2$: C, 35.6, H, 2.0; N, 6.9. Found: C, 35.3; H, 2.0; N, 6.5.

**3-Pyridinecarboxylic Acid.**—This compound was purchased from Reilly Tar and Chemical Corp. It had mp 234° (lit.[10] mp 236°).

*Anal.* Calcd for $C_6H_5NO_2$: C, 58.5; H, 4.1; N, 11.4. Found: C, 58.1; H, 4.0; N, 11.3.

**Preparation, Determination of Per Cent Composition and Kinetics of 2-Amino- and 2-Acetamido-3-pyridinecarboxylic Acid Mixture.**—This mixture was synthesized *via* acetylation[11] followed by oxidation[13] of 2-amino-3-methylpyridine. In the oxidation step partial hydrolysis of the amide linkage took place. The per cent composition was determined by titrating a given amount of sample with standardized NaOH and solving two simultaneous equations. The mixture was found to be 15% 2-acetamido-3-pyridinecarboxylic acid and 85% 2-amino-3-pyridinecarboxylic acid. The kinetics were run as described above; however, a twofold excess of the mixture was used as compared to the above acids in an effort to determine if any $CO_2$ was evolved. The reaction was run for over 1 hr. During this time no $CO_2$ was detected.

(8) R. H. Wiley and J. L. Hartman, *J. Amer. Chem. Soc.*, **73**, 494 (1951).
(9) E. V. Brown, *ibid.*, **76**, 3167 (1954).
(10) E. P. Oliveto, *Heterocycl. Compounds*, **14** (3), Chapter 10 (1962).
(11) S. M. McElvain, "The Characterization of Organic Compounds," Rev. Ed., Macmillan, New York, N. Y., 1964, p 210–201.
(12) L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 231 (1934).
(13) G. Ferrari and E. Marcon, *Educ. Sci.*, **14**, 594 (1959); *Chem. Abstr.*, **54**, 6709*a* (1960).

## Preparation and Photolysis of Esters of Perphthalic Acid[1]

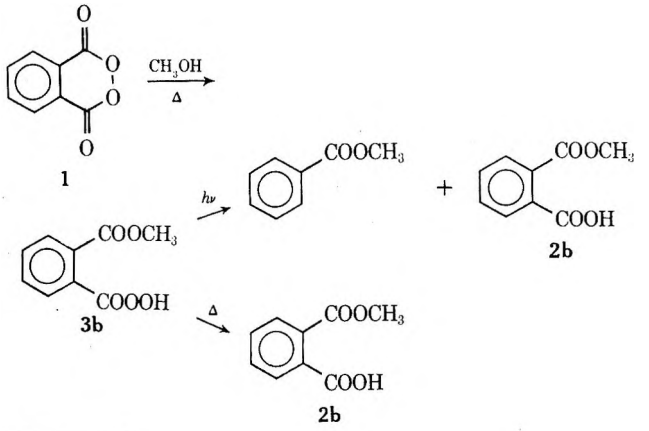
MARK R. DECAMP[2] AND MAITLAND JONES, JR.*

*Department of Chemistry, Princeton University, Princeton, New Jersey 08540*

*Received May 10, 1972*

Phthaloyl peroxide (**1**)[3,4a] has long been recognized as a highly reactive species. Greene and coworkers discovered the facile addition of **1** to unsaturated systems[4b–f] and attributed its reactivity to the inherent strain of a planar six-membered array containing a peroxide linkage. Horner and Brüggemann[5] studied thermal decompositions of **1** in a variety of substrates and found that the reactivity and rate of decomposition of **1** was considerably greater than that of its acyclic relative, benzoyl peroxide. Although they allude to the basic hydrolysis of **1**,[6] Horner and Brüggemann do not report any further reactions with hydroxylic oxygen nucleophiles. Greene[4a] also briefly mentioned the slow dissolution of **1** in water "with concomitant hydrolysis to monoperphthalic acid." We describe here the reaction of **1** with water and alcohols to give monoperphthalic acid and its esters. We further report the photolytic decomposition of these compounds.

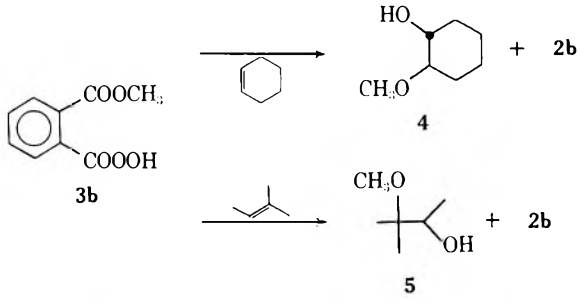
Upon overnight refluxing of **1** in methanol, a quantitative conversion to phthalic acid monomethyl ester (**2b**) was effected. Ester **2b** was identified by inspection of spectra, conversion to phthalic anhydride on gas chromatography, and formation of dimethyl phthalate



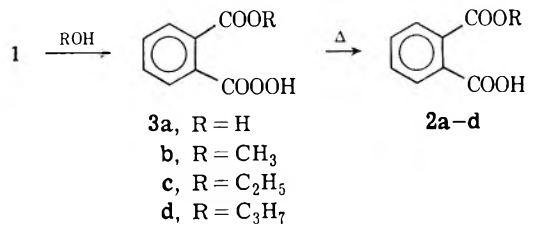

(1) Support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged (5528 AC1, 4).
(2) National Science Foundation Trainee, 1970–1971; Petroleum Research Fund Fellow, 1971–1972.
(3) K. E. Russell, *J. Amer. Chem. Soc.*, **77**, 4814 (1955).
(4) (a) F. D. Greene, *ibid.*, **78**, 2246 (1956); (b) *ibid.*, **78**, 2250 (1956); (c) F. D. Greene and W. W. Rees, *ibid.*, **80**, 3432 (1958); (d) F. D. Greene, *ibid.*, **81**, 1503 (1959); (e) F. D. Greene and W. W. Rees, *ibid.*, **82**, 890 (1960); (f) *ibid.*, **82**, 893 (1960).
(5) L. Horner and H. Brüggemann, *Justus Liebigs Ann. Chem.*, **635**, 22 (1960).
(6) Phthaloyl peroxide was dissolved in 0.1 *M* NaOH to form sodium phthalate and the sodium salt of monoperphthalic acid.

upon treatment with diazomethane. However, if **1** is merely dissolved in methanol and left to stand in the dark at room temperature, a new compound **3b** is formed. Formation of **3b** is rapid in neat methanol, but may be monitored conveniently by nmr spectroscopy in dilute solution. Mild thermolysis or photolysis converts **3b** to **2b**.

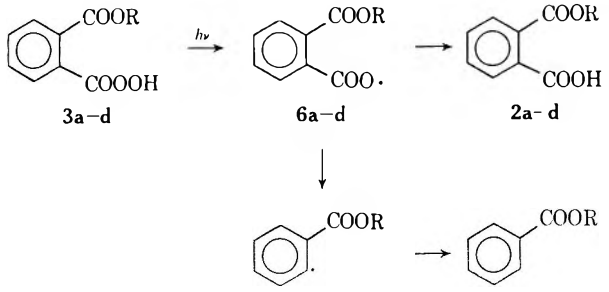
The new compound **3b** was identified as the methyl ester of perphthalic acid by the following spectral and chemical properties. The nmr spectrum of **3b** in $CCl_4$ contains an aromatic multiplet (δ 7.4–8.0, 4 H) and a singlet (δ 3.8, 3 H). Both the infrared spectrum (1735, 1700 $cm^{-1}$) and the ultraviolet spectrum (282, 276 nm) are very similar to the corresponding spectra of **2b**. Addition of cyclohexene or 2-methyl-2-butene to a methanolic solution of **3b** produced **2b** and the corresponding hydroxy ethers **4** and **5**. These latter compounds, which were presumably formed by methanolysis of an initially formed epoxide, were identified by comparison with authentic samples.




An entirely analogous reaction took place upon addition of water or other alcohols to **1**, as either monoperphthalic acid or the appropriate ester was formed. Although ortho-substituted perbenzoic acids are well known,[7] this appears to be the first report of an ester of perphthalic acid.




Irradiation of a methanolic solution of **1** through Pyrex with a 450-W medium-pressure mercury arc resulted in quantitative conversion to methylbenzoate and **2b**. A rational mechanism for this reaction involves decomposition of initially formed **3b**. Although the photolysis of perbenzoic acid itself seems not to have been reported, in our hands this process produced benzoic acid and benzene. Similarly the photolysis of *m*-chloroperbenzoic acid provided *m*-chlorobenzoic acid and chlorobenzene. A reasonable explanation for each of these reactions is that the oxygen–oxygen bond suffers photolytic cleavage to a benzoyloxy radical which is capable of hydrogen abstraction or decarboxylation. Peracetic acid has long been known as a photochemical source of hydroxy radicals.[8] The radical **6b** is also presumably the intermediate in the thermolysis of **1** in methanol.[9] Solutions of **1** in water, ethanol, and 1-propanol were also irradiated. In each case products analogous to those above were formed. Photolysis in 2-propanol followed a similar course, but in this case some products of the photodecomposition of **1**[11] were noted. Irradiation of **1** in *tert*-butyl alcohol resulted only in photolysis of the starting material. The latter two cases reflect an increasing inability to form perphthalate esters, presumably because of steric hindrance in the addition of the alcohol to **1**.




## Experimental Section[14]

**Phthaloyl Peroxide** (1).—The preparation of 1 by a modification of Greene's[4a] procedure has been described elsewhere.[12] Peroxide synthesized by this method is a fluffy white solid, mp 125° (lit.[4a] mp 126°). *Warning:* On one occasion freshly prepared 1 was detonated with explosive violence upon touching with a metal spatula. Prior to the explosion it had been noted that the peroxide was particularly crystalline. As with any peroxide, 1 should be handled with the utmost respect.

**Preparation of Esters of Monoperphthalic Acid (3b–d).**—1 (0.16 g, 1.0 mmol) was dissolved with stirring in 10 ml of the appropriate alcohol at room temperature. The crude esters could be obtained by removal of the solvent at reduced pressure, but no attempts were made to purify these potentially dangerous compounds. The esters were prepared and used *in situ* in the transformations which follow.

***trans*-2-Methoxycyclohexanol (4) and 3-Methoxy-3-methylbutan-2-ol (5).**—A methanolic solution of 1 was prepared as above. Several milliliters of cyclohexene were added and the solution was stirred for 1 hr at room temperature. Following concentration under reduced pressure, 4 was isolated by preparative glpc (retention time 2 min at 130°) and compared to an authentic sample. Compound 5 was formed by the same procedure using 2-methyl-2-butene as the substrate. It was isolated by preparative glpc (retention time 5 min at 90°), and compared to an authentic sample. Pure samples of 4 and 5 were prepared by the acid-catalyzed methanolysis of the corresponding epoxides.

**Photolyses of 3a–d.**—Alcoholic solutions of the esters of perphthalic acid (**3b–d**) were prepared as described above. A solu-

(7) D. Swern, Ed., "Organic Peroxides," Vol. I, Wiley, New York, N. Y., 1970, p 436.

(8) D. L. Heywood, B. Phillips, and H. A. Stansbury, Jr., *J. Org. Chem.*, **26**, 281 (1961).

(9) **6b** has been implicated in the thermolysis of the dimethyl ester of peroxydiphthalic acid.[10] In that study a major product was phthalic anhydride, which under our conditions would have been converted to the corresponding monoester of phthalic acid. However, either photolysis or thermolysis of the methyl ester **3b** in ethanol failed to produce any of the appropriate ethyl esters. Thus our results suggest that the radical **6b** is not prone to intramolecular cyclization.

(10) G. I. Nikishin, E. K. Starostin, and B. A. Golovin, *Bull. Acad. Sci. USSR, Ser. Chem.*, **5**, 869 (1971); *Izv. Akad. Nauk SSSR, Ser. Khim.*, **20**, 946 (1971).

(11) Photolysis of PPO in the presence of dilute alcohols affords phenylalkyl ethers from the addition of benzyne[12] to the alcohols, salicylate esters, phthalic acid, and benzoic acid.[13]

(12) M. Jones, Jr., and M. R. DeCamp, *J. Org. Chem.*, **36**, 1536 (1971).

(13) M. R. DeCamp, unpublished results.

(14) Nmr spectra were obtained with a Varian A-60A spectrometer using TMS as an internal standard; ir spectra were recorded on a Perkin-Elmer Model 237B spectrometer; uv spectra were measured with a Cary 14 recording spectrophotometer. Glpc analyses were performed on a Varian-Aerograph A90-P using a 1-m column of 10% DC 550 silicone oil on Chromosorb P.

tion of perphthalic acid (3a) itself was prepared by dissolving 0.16 g of 1 in aqueous acetone. All samples, 20 ml (0.05 *M*), were irradiated at room temperature through Pyrex with a Hanovia 450-W medium-pressure mercury arc. Following drying over $MgSO_4$, where appropriate, and concentration under reduced pressure, the crude photolysates were analyzed by nmr spectroscopy and glpc. Under our glpc conditions, phthalic acid and its half esters (2a–d) are quantitatively converted to phthalic anhydride. The presence of the carboxyl group was confirmed in separate runs by treating the crude photoproduct with an ethereal solution of diazomethane (prepared from *N*-methyl-*N*-nitrosourea) at 0° and observing the methyl ester by nmr spectroscopy.

**Registry No.**—3a, 2311-91-3; 3b, 36004-41-8.

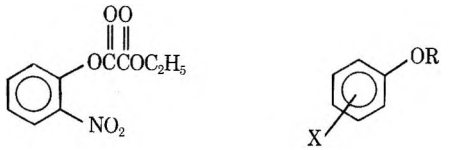
## Anomalous Ether Formation in Attempts to Transesterify Oxalate Esters with Phenoxides

EDWARD E. SMISSMAN,* MICHAEL D. CORBETT,[1] SAMIR EL-ANTABLY, AND KATHRYN C. KROBOTH

*Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044*

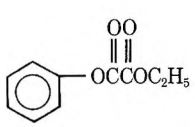
*Received April 10, 1972*

In an attempt to secure ethyl *o*-nitrophenyl oxalate (1) by transesterification, *o*-nitrophenol and diethyl oxalate were heated in dimethylformamide in the presence of a catalytic amount of potassium *o*-nitrophenoxide. The product isolated was not the desired mixed ester 1 but the ether, *o*-nitrophenetole (2), and potassium

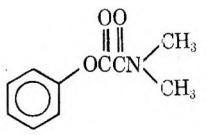




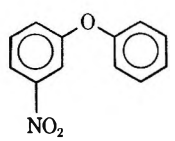
| | X | R |
|---|---|---|
| 1 | | |
| 2 | *o*-$NO_2$ | $C_2H_5$ |
| 3 | *m*-$NO_2$ | $C_2H_5$ |
| 4 | *p*-$NO_2$ | $C_2H_5$ |
| 5 | *p*-$C_6H_5CH_2$ | $C_2H_5$ |
| 6 | H | $C_2H_5$ |
| 7 | *o*-$NO_2$ | $CH(CH_3)_2$ |
| 8 | *p*-$C_6H_5CH_2$ | $CH(CH_3)_2$ |



9



10



11

monoethyl oxalate. It was initially assumed that this anomalous ether formation was due to neighboring group participation by the *o*-nitro function. However, under identical conditions, *m*-nitrophenol produced *m*-nitrophenetole (3), and *p*-nitrophenol gave *p*-nitrophenetole (4), thus eliminating the possibility of an ortho effect by the nitro group being involved in the reaction.

(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

The reaction is not limited to nitrophenols, since *p*-benzylphenol yielded *p*-benzylphenetole (5) and phenol gave phenetole (6) in good yields by the same process. The etherification also proceeded smoothly with diisopropyl oxalate to give *o*-isopropoxynitrobenzene (7). Di-*tert*-butyl oxalate would not undergo the reaction with *o*-nitrophenol under the conditions utilized for the etherification of the above compounds. At 150° di-*tert*-butyl oxalate decomposed[2] and no *tert*-butyl ether could be detected by tlc analysis on silica gel.

This reaction appears to be dependent on dimethylformamide, since the substitution of xylene or dimethyl sulfoxide as the solvent caused the reaction to fail.

Nucleophilic displacements of carboxylate anion from alkyl groups have been reported previously.[3–8] However, only the report by McDonough[8] describes an ether formation. On heating β-hydroxyethyl benzoate neat with an equimolar amount of diphenyl carbonate they produced β-phenoxyethyl benzoate. The scope and mechanism of this reaction was not investigated.

In order to determine if transesterification preceded ether formation, phenyl ethyl oxalate (9) was prepared and subjected to the conditions utilized for ether formation. When DMF was used as the solvent the half-ester half-amide 10 was obtained when either sodium methoxide or sodium ethoxide was used as the base. When sodium phenoxide was used, phenetole (6) was obtained and with sodium *m*-nitrophenoxide in DMF, *m*-nitrophenetole (3) was the product.

The above reactions were attempted using DMSO as the solvent and did not produce an isolable product.

Since the reaction requires DMF as a solvent it can be postulated that the solvent participates in the reaction. Phenyl ethyl oxalate (9) did not produce an ether when treated with either methoxide or ethoxide; therefore it can be concluded that transesterification does not precede ether formation.

The fact that diethyl oxalate and diisopropyl oxalate give rise to the corresponding alkyl phenyl ethers and that di-*tert*-butyl oxalate fails to give a product argues for a facile displacement reaction involving attack at the carbon attached to the ester ether oxygen. This is further substantiated in that *m*-nitrophenoxide when allowed to react with phenyl ethyl oxalate produces *m*-nitrophenetole (3) and not phenetole (6) or *m*-nitrophenyl phenyl ether (11).

From the above experiments a plausible mechanism (1) can be written.

### Experimental Section

Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses

(2) G. J. Karabatsos, J. M. Corbett, and K. L. Krumel, *J. Org. Chem.*, **30**, 689 (1965).

(3) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

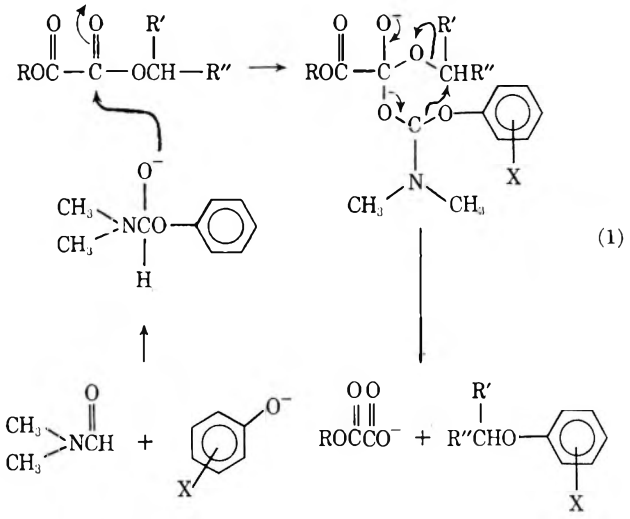
(4) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).

(5) P. A. Bartlett and W. S. Johnson, *ibid.*, 4495 (1970).

(6) L. J. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *J. Org. Chem.*, **36**, 1277 (1971).

(7) J. L. Kice, R. A. Bartsch, M. A. Dankleff, and S. L. Schwartz, *J. Amer. Chem. Soc.*, **87**, 1734 (1965).

(8) L. M. McDonough, *Chem. Ind. (London)*, 1501 (1965).



(1)

were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas. Unless specified otherwise, all spectra were consistent with the assigned structures.

*o*-**Nitrophenetole** (2).—*o*-Nitrophenol (7.0 g, 0.05 mol), potassium *o*-nitrophenoxide (0.9 g, 0.005 mol), and 30 ml of diethyl oxalate in 120 ml of DMF were heated to 120° for 12 hr. The dark reaction mixture was cooled and combined with 200 ml of $C_6H_6$. This solution was washed twice with 200 ml of $H_2O$ and dried ($Na_2SO_4$), and the solvent was removed *in vacuo* to give an on. Distillation at 72–74° (0.1 mm) gave 7.8 g (85%) of 2 as a yellow liquid, *m/e* 267.

*Anal.* Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 56.98; H, 5.32; N, 8.39.

This reaction was then performed with potassium *o*-nitrophenoxide (8.9 g, 0.05 mol) and no *o*-nitrophenol. The dark reaction mixture was cooled and a solid was collected by filtration. Partial purification was achieved by washing with $Et_2O$ to give potassium monoethyl oxalate as pale pink plates (5.5 g, 71%), mp 146–148°, ir (KBr) 1730 (ester C=O), 1645 $cm^{-1}$ (carboxylic acid anion C=O).

*m*-**Nitrophenetole** (3).—*m*-Nitrophenol (3.5 g, 0.025 mol) and NaH (0.12 g of a 53.4% suspension in mineral oil, 0.025 mol) were allowed to react in 60 ml of DMF. The solution was heated to 120° for 16 hr after the addition of 20 ml of diethyl oxalate. The dark reaction mixture was combined with 100 ml of $C_6H_6$ and washed with 100 ml of $H_2O$. The organic solution was dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to give an oil. Distillation gave a yellow oil, which solidified (2.7 g, 66%), mp 32–33° (lit. mp 34°).

*Anal.* Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.62; H, 5.71; N, 8.13.

*p*-**Nitrophenetole** (4).—By a procedure analogous to that used in the preparation of 3, *p*-nitrophenetole (4) was isolated as a yellow solid (2.1 g, 51%), mp 58.5–59.5° (lit. mp 60°).

*Anal.* Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.70; H, 5.35; N, 8.30.

*p*-**Benzylphenetole** (5).—*p*-Benzylphenol (9.2 g, 0.05 mol), NaH (0.23 g of a 54.4% suspension in mineral oil, 0.05 mol), and 30 ml of diethyl oxalate were heated to 120° in 120 ml of DMF for 24 hr. The reaction mixture was combined with 200 ml of $C_6H_6$ and washed twice with 200 ml of $H_2O$. The $C_6H_6$ solution was dried ($Na_2SO_4$) and the solvent was removed to give an oil. Distillation at 96–98° (0.1 mm) gave 6.9 g (60%) of 5 as a colorless oil.

*Anal.* Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.59. Found: C, 84.89; H, 7.83.

*p*-**Benzylphenyl Isopropyl Ether** (8).—*p*-Benzylphenol (9.2 g, 0.05 mol), NaH (0.23 g of a 54.4% suspension in mineral oil, 0.05 mol), and 30 ml of diisopropyl oxalate were heated to 130° in 120 ml of DMF for 24 hr. The reaction mixture was combined with 200 ml of $C_6H_6$ and washed twice with 200 ml of $H_2O$. The $C_6H_6$ solution was dried ($Na_2SO_4$) and the solvent was removed to give an oil. Distillation at 102° (0.2 mm) gave 6.8 g (60%) of 8 as a colorless oil.

**Phenyl Ethyl Oxalate** (9).—Phenol (28.2 g, 0.3 mol) in 100 ml of dioxane was added slowly to a cold suspension of NaH (12.63 g of a 53.4% suspension in mineral oil, 0.3 mol) in 200 ml of dioxane. After the solution was stirred for 10 min, 41 g (0.3 mol) of ethyloxalyl chloride was added slowly. The mixture was refluxed for 45 min, cooled, and filtered, the solvent was removed, and the residue was distilled at 100–105° (0.2 mm) to give 40 g (69%) of a colorless oil.

**Reactions of Phenyl Ethyl Oxalate. A. With Sodium Methoxide in DMF.**—Sodium methoxide (2.16 g, 0.04 mol) in 50 ml of DMF was allowed to react with 3.88 g (0.02 mol) of the diester in 50 ml of DMF. The mixture was heated at 120° for 12 hr. On cooling, 200 ml of benzene was added, the solution was washed with $H_2O$ and aqueous $NaHCO_3$ and dried ($Na_2SO_4$), and the benzene was removed to yield an oil. The oil was found to be the phenyl half-ester *N,N*-dimethylamide of oxalic acid 10.

**B. With Sodium Ethoxide in DMF.**—The conditions and product were identical with those of procedure A.

**C. With Sodium Phenoxide in DMF.**—Sodium phenoxide (4.64 g, 0.04 mol) and the diester (3.88 g, 0.02 mol) were heated at 120° in 100 ml of DMF for 12 hr. The mixture was treated with 200 ml benzene, washed with $H_2O$, 10% NaOH, and water, and dried ($Na_2SO_4$) and the solvent was removed to give 2.4 g (50%) of phenetole (6).

**D. With Sodium *m*-Nitrophenoxide in DMF.**—Utilizing sodium *m*-nitrophenoxide (5.4 g, 0.04 mol) in a procedure identical with C, 2.7 g (40%) of *m*-nitrophenetole was obtained.

**Registry No.**—2, 610-67-3; 3, 621-52-3; 4, 100-29-8; 5, 35672-52-7; 8, 35672-53-8; 9, 15779-81-4; potassium monoethyl oxalate, 1906-57-6.

**Acknowledgment.**—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grant GM-01341 and the National Science Foundation URP Grant GY-6103.

## Dehalogenation of Organic Halides by Titanocene

ASHOT MERIJANIAN*[1] AND THOMAS MAYER

*Department of Chemistry, William Paterson College, Wayne, New Jersey 07470*

JOHN F. HELLING AND FRED KLEMICK[2]

*Departments of Chemistry and Physical Sciences, University of Florida, Gainesville, Florida 32601*

*Received December 29, 1971*

The synthesis, some structural studies, and a relatively small number of chemical reactions of titanocene [$(C_{10}H_{10}Ti)_2$] have been reported.[3] Although Watt and coworkers observed that titanocene reacted with various halogenated organic solvents, the products were not investigated. We now wish to report that titanocene is useful in effecting dehalogenation of a number of organic halides. We have found that titanocene can abstract halogens readily at room temperature from alkyl, allyl, and certain vinyl halides but not from aromatic halides. In all the dehalogenation reactions coupling and/or unsaturated products resulted from the organic halides and stable green halide complexes were formed from titanocene. The successful dehalogenations where the organic products were isolated are summarized in Table I.

(1) Member of 1969 National Science Foundation Summer Research Participation Program for College Teachers at the University of Florida and Recipient of an NSF-RPCT extention Grant 1969–1971.

(2) National Science Foundation Undergraduate Summer Research Participation Program, 1969.

(3) "Advances in Organometallic Chemistry," Vol. 9, F. G. A. Stone and R. West, Ed., Academic Press, New York, N. Y., 1970. pp 175–179.

TABLE I
REACTIONS OF TITANOCENE WITH ORGANIC HALIDES

| Organic halide | Registry no. | Mole ratio of titanocene:halide[a] | Product | Yield, %[b] |
|---|---|---|---|---|
| 1,2-Dibromocyclohexane | 5401-62-7 | 1.0:1.0 | Cyclohexene | 42.5 |
| Benzyl chloride | 100-44-7 | 1.0:1.0 | Dibenzyl | 18.6 |
| Benzal chloride | 98-87-3 | 1.0:3.6 | *cis*-Stilbene | 2.9 |
| | | | *trans*-Stilbene | 14.0 |
| | | | *dl*-Stilbene dichloride | 9.2 |
| Benzotrichloride | 98-07-7 | 1.0:2.0 | *cis*-Dichlorostilbene | 15.9 |
| | | | *trans*-Dichlorostilbene | 8.9 |
| | | | 1,2-Diphenyl-1,1,2,2-tetrachloroethane | 7.0 |
| | | | Biphenyl[c] | |
| *meso*-Stilbene dichloride | 15951-99-2 | 1.0:1.0 | *trans*-Stilbene | 64.0 |
| *meso*-Stilbene dibromide | 13440-24-9 | 1.0:1.0 | *trans*-Stilbene | 73.6 |
| *trans*-1,2-Dibromostilbene | 20432-10-4 | 1.0:2.0 | Diphenylacetylene | 23.2 |
| *trans*-1,2-Diiodostilbene | 20432-11-5 | 1.0:2.0 | Diphenylacetylene | 34.2 |

[a] Mole ratio calculations are based on titanocene *monomer*. [b] Yields were based on the assumption of abstraction of two halogen atoms per titanium atom of titanocene. Theoretical yields of individual products were based on the assumption that they were the sole products. [c] No yield was calculated for this product. See Experimental Section for the extent of its formation.

The aromatic halides which titanocene failed to dehalogenate included *o*-dichlorobenzene, *o*-dibromobenzene, *p*-nitrobromobenzene, and *p*-bromoanisole. In all these cases the starting materials were recovered following reaction attempts under different conditions.

Of the green complexes formed by titanocene in the dehalogenation reactions, the chloro complex proved to have the greatest air stability. Regardless of the organic chlorine compound used, it analyzed consistently for a formula of $C_{20}H_{19}Ti_2Cl_4$. Based on this formula the yields of the titanium product were usually almost quantitative. This compound is not monomeric judging from its insolubility in the common solvents. Reproducible elemental analyses could not be obtained for the somewhat less stable analogous bromide complexes, but the data and other observations suggest a similar dimeric structure.

The mechanisms of these reactions have not been established.

## Experimental Section

**Materials.**—Titanocene was synthesized by the method described by Watt, Baye, and Drummond[4] and used without sublimation. The organic halides were purified by recrystallization or fractional distillation till they had sharp melting points or were gas chromatographically pure. All solvents (benzene, THF, toluene, pentane) were distilled over calcium hydride, $LiAlH_4$, or Na–K alloy and stored under argon.

**Analyses.**—Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Fritz-Pregl-Strasse, West Germany. Gas chromatographic analyses were carried out on a Hewlett-Packard F & M Model 5754B gas chromatograph using 6 ft × 0.125 in., SE-30 columns.

**Apparatus.**—All the dehalogenations were carried out in a 100-ml, round-bottom, three-necked flask equipped with reflux condenser, constant pressure dropping funnel, magnetic stirrer, and an inlet for argon free of oxygen or moisture. The apparatus was evacuated, flame dried, and filled with argon prior to each reaction.

**Calculations.**—A mole of titanocene was based on the monomer, $C_{10}H_{10}Ti$, for mole ratio and per cent yield calculations. The theoretical yields are based on the assumption of abstraction of two halogen atoms per titanium atom in titanocene and the formation of $C_{20}H_{19}Ti_2X_4$ complexes.

**Reaction of Titanocene with 1,2-Dibromocyclohexane.**—Titanocene (5.0 g, 28 mmol) was stirred in 15 ml of toluene, and a solution of 1,2-dibromocyclohexane (6.45 g, 26.7 mmol) in 25 ml of toluene was added dropwise within 10 min. After an initial exothermic period the reaction was continued for 24 hr at room temperature. Volatiles were vacuum distilled from the flask and collected in a Dry Ice–acetone cooled receiver. The residue, a stable greenish solid, weighed 9.0 g (95%) after drying. The distillate was fractionally distilled in a spinning band column and fractions boiling at 80–82, 82–85, and 85–108° were collected. These fractions were found by gas chromatography to contain 99, 79, and 8% cyclohexene, respectively. These correspond to a total of 0.93 g of cyclohexene (42.5% yield) based on the calibration of the chromatograph.

**Reaction of Titanocene with Benzyl Chloride.**—To titanocene (1.0 g, 5.6 mmol) stirred in 15 ml of benzene, a solution of benzyl chloride (1.43 g, 11.3 mmol) in 5 ml of benzene was added dropwise. The reaction mixture was then stirred for 12 hr at room temperature. The contents were then exposed to air and filtered. The green filter cake was further washed with benzene and petroleum ether (bp 30–60°). The insoluble, green solid weighed 1.38 g (99%) after drying under vacuum. The filtrate was concentrated, reslurried in pentane, and passed through a silica gel column. From the concentrated, cooled eluate crystals were separated and recrystallized from pentane. After drying, the purified crystals, identified as dibenzyl, weighed 0.19 g (mp 52–52.5°), corresponding to a yield of 18.6%.

**Reaction of Titanocene with Benzal Chloride.**—To a well-stirred slurry of titanocene (4.00 g, 22.4 mmol) in 20 ml of pentane was added a solution of benzal chloride (13.00 g, 80.0 mmol) in 10 ml of pentane within a 10-min period. The reaction was exothermic. The contents were stirred for 16 hr at room temperature, exposed to air, and filtered. The green filter cake was washed several times with pentane and dried under vacuum. The filtrate was distilled under vacuum to remove the pentane and the excess benzal chloride. The residue was treated with hot pentane and filtered. Evaporation of the filtrate gave a residue weighing 1.35 g which was shown (gc, ir) to consist of 4.3% *cis*-stilbene, 20.9% *trans*-stilbene, 38.2% *dl*-stilbene dichloride, and 34.6% benzal chloride.

The dried, insoluble green solids were extracted by benzene in a Soxhlet extraction apparatus, dried (4.30 g, 77%), and analyzed.

*Anal.* Calcd for $C_{20}H_{19}Ti_2Cl_4$: C, 48.34; H, 3.85; Ti, 19.28; Cl, 28.53. Found: C, 48.02; H, 3.86; Ti, 19.52; Cl, 28.23.

**Reaction of Titanocene with Benzotrichloride.**—A solution of benzotrichloride (11.80 g, 60.2 mmol) in 18 g of THF was slowly added dropwise to titanocene (5.35 g, 30.0 mmol) in THF (18 g). After the initial exothermic reaction, the mixture was stirred for 8 hr at room temperature and then exposed to air and evaporated to dryness. The residue was extracted with boiling pentane several times and the remaining insoluble green solid was dried under vacuum (7.5 g, 100%). The pentane extracts were combined and the pentane was removed. The residue (2.10 g) consisted (gc, ir) of 28.2% *cis*-dichlorostilbene, 15.8% *trans*-dichlorostilbene, 32.0% 1,2-diphenyl-1,1,2,2-tetrachloroethane, 13.4% biphenyl,[5] and 10.6% of the starting benzotrichloride.

(4) G. W. Watt, L. J. Baye, and F. O. Drummond, Jr., *J. Amer. Chem. Soc.*, **88**, 1139 (1966).

(5) Biphenyl, which was not present in the reactants, was produced in carefully repeated experiments; its mode of formation is presently unknown.

After additional extraction of impurities with benzene in a Soxhlet extraction apparatus and drying, the green solid was submitted for elemental analysis.

*Anal.* Calcd for $C_{20}H_{19}Ti_2Cl_4$: C, 48.34; H, 3.85; Ti, 19.28; Cl, 28.53. Found: C, 48.39, 48.43; H, 3.83, 3.84; Ti, 19.34, 19.35; Cl, 28.31, 28.33.

**Reaction of Titanocene with *meso*-Stilbene Dichloride.**—*meso*-Stilbene dichloride (0.50 g, 2.0 mmol) and 9 ml of benzene were added separately to a solution of titanocene (0.36 g, 2.0 mmol) in 5 ml of benzene with stirring. The reaction was exothermic with considerable foaming. After the reaction mixture had been stirred for 24 hr at room temperature, the contents were exposed to air and filtered. The green filter cake was washed with benzene and dried; it weighed 0.4 g (80%). The filtrate was evaporated to dryness and the residue was extracted with boiling petroleum ether. From the combined extracts three crystalline crops were collected, combined, and dried under vacuum. The dry, flaky crystals, which were identified as *trans*-stilbene, were recrystallized from petroleum ether. The final product weighed 0.23 g, mp 122–124° (lit.[6] mp 124°), corresponding to a yield of 64.0%.

**Reaction of Titanocene with *trans*-Diiodostilbene.**—Benzene (30 ml) was added to a solid mixture of titanocene (1.20 g, 6.74 mmol) and *trans*-diiodostilbene (1.45 g, 3.36 mmol). The mixture was stirred for 24 hr at room temperature. The contents were then filtered and the brownish-green filter cake was washed with benzene. The filtrate was evaporated to dryness and the residue was extracted with boiling pentane. The pentane extracts were combined and evaporated. The remaining residue was recrystallized from pentane and dried. The product, identified as diphenylacetylene, weighed 0.41 g, mp 60–61° (lit.[7] mp 64°), corresponding to a yield of 34.2% based on titanocene and 68.6% based on *trans*-diiodostilbene used in the reaction.

**Registry No.**—Titanocene, 1271-29-0.

(6) "Handbook of Chemistry and Physics," 48th ed, Chemical Rubber Co., Cleveland, Ohio, 1967, p C-546.

(7) Reference 6, p C-321.

## Preparation of *N,N*-Bis(2-fluoro-2,2-dinitroethyl)amides

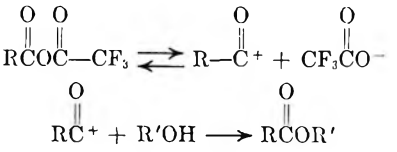
WILLIAM H. GILLIGAN

*Advanced Chemistry Division, U. S. Naval Ordnance Laboratory, White Oak, Silver Spring, Maryland 20910*

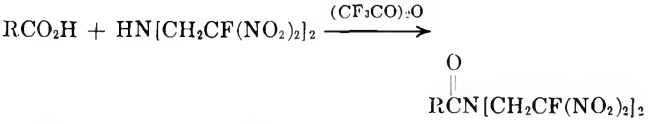
*Received April 4, 1972*

In a recent paper by Adolph and Kamlet[1] the preparation of bis(2-fluoro-2,2-dinitroethyl)amine (**1**) was reported. These authors showed that **1** was weakly basic; it could be recrystallized unchanged from trifluoroacetic acid, was insoluble in 50% sulfuric acid, and did not form isolable salts with mineral acids.[2] The weak nucleophilic properties of the amine **1** toward protons appear to parallel equally weak nucleophilic properties toward carbon. Attempts to prepare amides by the reaction of **1** with anhydrides or acyl chlorides or by ester amination, under usual conditions, proved fruitless.

Mixed trifluoroacetic–carboxylic anhydrides have been extensively used as mild reagents for preparing esters.[3] It has been postulated that the reactive species is the acylium ion, formed in equilibrium with the mixed anhydride.[4] In contrast, the main reaction



course with amines involves a nucleophilic attack directly on the mixed anhydride, forming the trifluoroacetamide as the predominant product.[5] Thus, the method has been considered unsuitable for N-acylation.[3a] It seemed likely, however, that bis(fluorodinitroethyl)amine **1**, because of its lack of basic properties, would react *via* an acylium ion mechanism, if it reacted at all. Therefore an investigation of the reaction of mixed anhydrides with **1** was undertaken.



Bis(fluorodinitroethyl)amine **1** reacted at ambient temperature with the mixed anhydride formed by the addition of acetic acid to trifluoroacetic anhydride. The reaction, as judged by tlc analysis,[6] was complete and essentially quantitative in 24 hr. The reaction time for the mixed anhydride of butyric acid was 48 hr and for isobutyric acid 192 hr at ambient temperature. Pivalic acid was completely unreactive. That steric factors can play an important and even overriding role is not unexpected in view of the bulky nature of the amine.

With acrylic acid, a 69% yield of *N,N*-bis(2-fluoro-2,2-dinitroethyl)acrylamide (**5**) was obtained after 4 days at ambient temperature. Fumaric and succinic acid did not react under these conditions, presumably because of the formation of the unreactive cyclic anhydrides.[3a] Ethyl fumarate, however, gave a 44% yield of ethyl *N,N*-bis(2-fluoro-2,2-dinitroethyl)fumaramate (**6**) after 5 days at 80°. Chloroacetic acid required a longer reaction period of 25 days at 80°, while dichloroacetic acid was unreactive at 100° for periods up to 13 days. In contrast to dichloroacetic acid, a 71% yield of ethyl *N,N*-bis(2-fluoro-2,2-dinitroethyl)oxamate was isolated from the reaction of the mixed anhydride of ethyl oxalate with **1** after 5 days at 100°.

For an acylium ion mechanism it would be expected that electronegative substituents on the carboxylic acid would inhibit the reaction by lowering the equilibrium concentration of both the mixed anhydride and the acylium ion. In general the experimental results are in accord with this expectation. However, an examination of the collected results in Table I indicates that ethyl oxalate reacts more readily than would be anticipated on the basis of inductive effects. The

(1) H. G. Adolph and M. J. Kamlet, *J. Org. Chem.*, **34**, 45 (1969).

(2) A $pK_a$ value of 0.4 can be calculated for **1** using Hall's correlation equation for secondary amines (ref 2a) and a $\sigma^*$ value of 1.57 for the fluorodinitroethyl group (ref 2b). However, the data of Bagal and coworkers (ref 2c) indicates that amines substituted with bulky nitro groups are less basic than would be expected solely on the basis of inductive effects. A more reasonable figure for the $pK_a$ of **1** would be $\sim -0.3$. (a) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1951). (b) L. A. Kaplan and H. B. Pickard, *J. Org. Chem.*, **35**, 2004 (1970). (c) L. I. Bagal, G. I. Koldobskii, and E. S. Gerasimova, *Zh. Org. Khim.*, **3**, 2084 (1967).

(3) (a) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955); (b) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965); L. Alimirante and G. Tosolini, *ibid.*, **26**, 177 (1961).

(4) For a comprehensive discussion of the possible equilibria involved in mixed anhydrides see ref 3a.

(5) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

(6) W. H. Gilligan, *J. Org. Chem.*, **36**, 2138 (1971).

TABLE I

PREPARATION OF *N,N*-BIS(2-FLUORO-2,2-DINITROETHYL)CARBOXAMIDES $RC(=O)N[CH_2CF(NO_2)_2]_2$

| Compd | $RCO_2H$, R = | $\sigma_R^{*a}$ | Reaction conditions: Molar ratio of reactants Amine 1: Acid:TFAA | Temp, °C | Time, days | Yield, % | Mp, °C | Anal.[b] % C | H | F | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | $CH_3$ | 0.0 | 1:2.5:4.0 | Ambient | 1 | 82 | 77–78 | 21.76 | 2.13 | 11.48 | 21.15 |
| | | | | | | | | 21.96 | 2.11 | 11.63 | 21.05 |
| 3 | $CH_3CH_2CH_2$ | −0.12 | 1:2.5:4.0 | Ambient | 2 | 98 | 55–56 | 26.75 | 3.09 | 10.58 | 19.50 |
| | | | | | | | | 26.69 | 3.01 | 10.44 | 19.36 |
| 4 | $(CH_3)_2CH$ | −0.13 | 1:2.5:4.0 | Ambient | 8 | 92 | 64–65 | 26.75 | 3.09 | 10.58 | 19.50 |
| | | | | | | | | 26.61 | 2.99 | 10.52 | 19.60 |
| | $(CH_3)_3C$ | −0.30 | 1:2.5:4.0 | Ambient | >30 | | | | | | |
| 5 | $H_2C=CH$ | 0.36 | 1:6.1:6.1 | Ambient | 4 | 69 | 111–113 | 24.50 | 2.06 | 11.07 | 20.41 |
| | | | | | | | | 24.45 | 2.08 | 11.22 | 20.06 |
| 6 | $EtO_2CCH:CH$ | 0.62 | 1:4.3:4.3 | 80 | 5 | 44 | 85–86 | 28.92 | 2.67 | 9.15 | 16.87 |
| | | | | | | | | 28.83 | 2.73 | 9.02 | 16.62 |
| 7 | $ClCH_2$ | 1.05 | 1:4.0:4.0 | 80 | 25 | 42 | 87–88 | 19.71 | 1.66 | 10.39 | 19.16 |
| | | | | | | | | 19.60 | 1.43 | 10.16 | 18.84 |
| 8 | $EtO_2C$ | 2.00 | 1:4.3:4.3 | 80 | 5 | 41 | 73–74 | 24.69 | 2.33 | 9.76 | 18.00 |
| | | | 1:4.3:4.3 | 100 | 5 | 71 | | 24.55 | 2.18 | 9.58 | 18.04 |
| | $Cl_2CH$ | 1.94 | 1:4.3:4.3 | 100 | 13 | | | | | | |

[a] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13. [b] Upper line, calculated value; lower line, experimental value.

TABLE II

INFRARED AND PMR ABSORPTION BANDS OF *N,N*-BIS(2-FLUORO-2,2-DINITROETHYL)CARBOXAMIDES

| Compd | $RCON[CH_2CF(NO_2)_2]_2$ R = | Ir, $cm^{-1}$: CO (amide 1) | CO (ester) | Pmr, δ[a]: $FCCH_2$ | $CH_3$ | $CH_2$ | $H_c$, $H_b(CO_2Et)$, $C=C$, $H_a$ | Miscellaneous |
|---|---|---|---|---|---|---|---|---|
| 2 | $CH_3$ | 1703 | | 4.80 (d) | 2.22 (s) | | | |
| 3 | $CH_3CH_2CH_2$ | 1697 | | 4.80 (d) | 0.95 (t) | 1.66 (m) | | |
| | | | | | | 2.34 (t) | | |
| 4 | $(CH_3)_2CH$ | 1691 | | 4.80 (d) | 1.15 (d) | | | 2.75 (m, CH) |
| 5 | $H_2C=CH$ | 1685 | | 5.15 (d) | | | 6.76 (m, $H_c$) | |
| | | | | | | | 6.46 (d), 6.29 (d, $H_a$) | |
| | | | | | | | 5.98 (d), 5.88 (d, $H_b$) | |
| 6 | $EtO_2CCH=CH$ | 1687 | 1728 | 4.89 (d) | 1.30 (t) | 4.24 (q) | 7.17 (d, $H_c$) | |
| | | | | | | | 6.85 (d, $H_a$) | |
| 7 | $ClCH_2$ | 1705 | | 4.90 (d) | | 4.33 (s) | | |
| 8 | $EtO_2C$ | 1708 | 1744 | 5.01 (q) | 1.42 (t) | 4.41 (q) | | |

[a] s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.

reason for this apparent discrepancy is not obvious and further investigation appears warranted.

Collected in Table II are the ir and pmr absorption bands for the carboxamides **2**–**8**. The CO (amide 1) band for *N,N*-bis(fluorodinitroethyl)acrylamide **5** is at 1685 $cm^{-1}$ and for ethyl *N,N*-bis(fluorodinitroethyl)-fumaramate **6** at 1687 $cm^{-1}$, indicating that there may be a small shift of about 10 $cm^{-1}$ to lower frequencies owing to conjugation. This effect is more apparent for the CO (ester) band of **6**. For the other compounds, the CO (amide 1) band falls in the range 1691–1708 $cm^{-1}$. The $NO_2$ asymmetric stretching vibration (1604–1613 $cm^{-1}$),[7] the $NO_2$ symmetric stretching vibration (1310–1315 $cm^{-1}$),[7] and the C–N modes (849–852 and 805–807 $cm^{-1}$)[7] were within the ranges expected for fluorodinitroethyl compounds.[8] The *trans*-CH=CH out-of-plane deformation vibration appeared at 974 $cm^{-1}$ for **6**.

(7) Not shown in Table II.

(8) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

The pmr spectra showed a broadened doublet ($FCCH_2$, $J_{HF}$ = 13 ± 0.5 Hz) at 4.80–5.15 ppm for compounds **2**–**7**. Ethyl *N,N*-bis(2-fluoro-2,2-dinitroethyl)-oxamate (**8**) exhibited a broadened quartet at 5.01 ppm ($J_{HF}$ = 13 Hz). The olefinic protons of the acrylamide **5** showed a typical ABX pattern ($J_{H_aH_c}$ = 17, $J_{H_bH_c}$ = 10, $J_{H_aH_b}$ = 2 Hz) and of the fumaramate **6** a simple *trans*-HH pattern ($J_{HH}$ = 15 Hz). For the latter compound there was no indication of any band that could be correlated with the *cis*-CH=CH structural moiety. Other absorption bands associated with $CH_2$ and $CH_3$ groups are unexceptional with $J_{HH}$ values of 7 ± 0.5 Hz. Area ratios corresponded to the assigned structures.

There are a large number of both aliphatic and aromatic amines of low basicity. It would seem, based on these results, that many would be suitable compounds for N-acylation by mixed anhydrides, contrary to statements in the literature.

### Experimental Section

**General (Caution).**—The polynitro compounds described in this paper are explosives and should be handled with due care. In particular, reactions, should be run on a small scale (1 or 2 g) behind adequate shielding with careful attention to temperature control. Handling of hot reaction vessels should be strictly avoided. Personnel should be equipped with full face masks, heavy rubber gloves, and fire-retardant laboratory coats.

Pmr spectra were obtained in deuteriochloroform solution with tetramethylsilane as the internal standard using a Varian HA-100 spectrometer. Infrared spectra were obtained in 1,2-dichloroethane solution using a Beckman IR-4 spectrometer. Melting points are uncorrected.

**General Directions for Preparing *N*,*N*-Bis(2-fluoro-2,2-dinitroethyl)amides.**—The reactants in the proportions given in Table I were combined in a stoppered flask and stirred magnetically until the amine 1 was dissolved. The flask was then allowed to stand at ambient temperature for the indicated time, while samples were withdrawn periodically to monitor the course of the reaction by tlc. For reactions run at higher temperatures the flask was equipped with a reflux condenser topped with a drying tube filled with calcium sulfate.

After the indicated time had elapsed, the crude mixture was taken up in methylene chloride and washed consecutively with water, 0.4 *N* NaOH, and water. After drying with magnesium sulfate and filtering, volatiles were removed *in vacuo*. If crystallization did not occur spontaneously, the crude product was purified by column chromatography on silica gel (G. Frederick Smith Co., 50–200 mesh). Benzene was used as the eluent. Recrystallization was from methylene chloride or methylene chloride–carbon tetrachloride mixtures.

**Registry No.**—**2**, 35666-43-4; **3**, 35666-44-5; **4**, 35666-45-6; **5**, 35666-46-7; **6**, 35666-47-8; **7**, 35666-48-9; **8**, 35666-49-0.

---

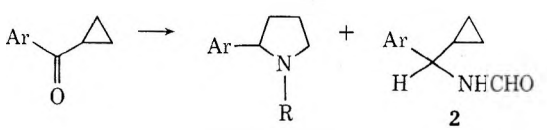
## The Synthesis of *cis*- and *trans*-1-Methyl-2,5-diphenylpyrrolidines by the Leuckart Reaction of 1-Benzoyl-2-phenylcyclopropane[1]

ELI BREUER* AND DAVID MELUMAD

*Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel*

*Received March 8, 1972*

Previously we reported that the Leuckart reaction of cyclopropyl aryl ketones with formamide gives predominantly the rearranged products 1-formyl-2-arylpyrrolidines (**1a**), in addition to small amounts of the



**1a**, R = CHO
**b**, R = $CH_3$

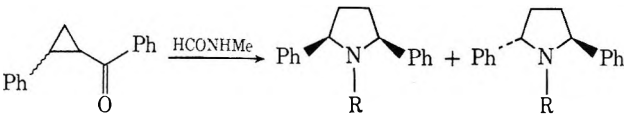
normal products (**2**).[2] Subsequently we observed that the reaction of *N*-methylformamide with cyclopropyl phenyl ketone, which proceeds considerably more slowly than that of the formamide, occurs with exclusive rearrangement, giving in high yield 1-methyl-2-phenylpyrrolidine (**1b**, Ar = Ph).[3] Using this reaction we achieved a one-step synthesis of nicotine (**1b**, Ar = 3-pyridyl) from cyclopropyl 3-pyridyl ketone.[3]

In this paper we wish to describe results obtained from the Leuckart reaction of 1-benzoyl-2-phenylcyclopropane with *N*-methylformamide. This work was undertaken to study the direction of the cyclopropane ring opening and the stereochemistry of the reaction.

### Results

A mixture of *cis*- and *trans*-1-benzoyl-2-phenylcyclopropane (**3**) was obtained from the reaction of benzalacetophenone and dimethylsulfoxonium methylide.[4] This mixture of stereoisomeric ketones was heated to 180° with *N*-methylformamide in the presence of catalytic amounts of magnesium chloride for 25 hr. After this period of time gas chromatographic analysis indicated the absence of ketone and the presence of two products in the ratio of 2:1, in a total yield of 50%.

The products were separated by chromatography on silica gel. The major component was identified as *cis*-1-methyl-2,5-diphenylpyrrolidine (**4b**), while the minor component was found to be the trans isomer (**5b**).



**3** **4a**, R = H; **b**, R = Me **5a**, R = H; **b**, R = Me

These structure assignments were confirmed by independent syntheses. Thus we have prepared *cis*- and *trans*-2,5-diphenylpyrrolidine[5] (**4a** and **5a**, respectively), which were converted to the respective *N*-methyl derivatives (**4b** and **5b**) by formic acid–formaldehyde. The *cis*- and *trans*-1-methyl-2,5-diphenylpyrrolidines so obtained were found identical in every respect with the products obtained in our reaction. Nmr data are given in Table I.

In order to study the possible influence of the stereochemistry of starting material, we have prepared pure *cis*-1-benzoyl-2-phenylcyclopropane.[6] Reaction of this ketone with *N*-methylformamide yielded a mixture of **4b** and **5b** in the same yield and ratio as those obtained in the previous reaction.

The absence of 2,4-diphenylpyrrolidines was confirmed by comparison of the product mixture with samples prepared by a known reaction.[7]

The formation of products **4b** and **5b** can be rationalized by assuming that attack of *N*-methylformamide upon the carbonyl group of **3** produces a hydroxyformamide type intermediate[8] which dissociates to an

(1) A preliminary account of this study was presented at the 39th Meeting of the Israel Chemical Society, Jerusalem, Sept 29–Oct 1, 1969. E. Breuer and D. Melumad, *Israel J. Chem.*, **7**, 31 (1969).

(2) E. Breuer and Y. Stein, *ibid.*, **6**, 901 (1968).

(3) E. Breuer and D. Melumad, *Tetrahedron Lett.*, 3595 (1969).

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

(5) C. G. Overberger, M. Valentine, and J. P. Anselme, *ibid.*, **91**, 687 (1969).

(6) H. M. Walborsky and L. Plonsker, *ibid.*, **83**, 2138 (1961).

(7) M. C. Kloetzel, *ibid.*, **69**, 2271 (1947).

(8) M. L. Moore, *Org. React.*, **5**, 301 (1949).

TABLE I

NMR DATA OF *cis*- AND *trans*-2,5-DIPHENYLPYRROLIDINES AND THEIR *N*-METHYL DERIVATIVES[a]

| Compd | Aromatic (10 H) | Benzylic (2 H) | *N*-Methyl (3 H) |
|---|---|---|---|
| **4a** | 7.27 | 4.25 | |
| **5a** | 7.23 | 4.43 | |
| **4b** | 7.31 | 3.34 | 1.98 |
| **5b** | 7.22 | 4.10 | 1.88 |

[a] Given in δ values; $CDCl_3$ solution with TMS as internal standard.

immonium–carbonium ion that is capable of rearranging to a pyrroline derivative.[9,10] The latter is reduced *in situ* by formic acid to products **4b** and **5b**.[11] The predominant formation of the cis product **4b** is in agreement with what is known concerning the stereochemistry of the Leuckart reaction.[12]

### Experimental Section[13]

**1-Benzoyl-2-phenylcyclopropane** (**3**) (a mixture of isomers) was prepared by the action of dimethylsulfoxonium methylide on benzalacetophenone,[4] mp 45–50° (lit.[4] mp 45.5–50.0°). The spectral properties of the material were in agreement with those published.[4]

***cis*-1-Benzoyl-2-phenylcyclopropane** was prepared by the action of phenyllithium on *cis*-2-phenylcyclopropanecarboxylic acid, mp 68–70° (lit.[6] mp 69–70°).

**Reaction of *N*-Methylformamide with 1-Benzoyl-2-phenylcyclopropane.**—A mixture of 5.5 g (0.025 mol) of ketone, 9 g of *N*-methylformamide, and 0.22 g (0.0025 mol) of $MgCl_2 \cdot 2H_2O$ was heated in an oil bath at 180° for 24 hr under $N_2$. The reaction mixture was dissolved in dilute hydrochloric acid and extracted several times with ether. The aqueous acidic solution was made alkaline by the addition of sodium hydroxide, and extracted five times with ether. After drying, the ether was evaporated to give a residue (2.5 g). This mixture was separated by chromatography on silica gel. Elution with benzene gave pure *cis*-1-methyl-2,5-diphenylpyrrolidine (**4b**), mp 60° (1.6 g). The compound was further purified by collecting a sample by preparative gas chromatography.

*Anal.* Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.47; H, 8.04; N, 5.75.

The picrate had mp 152° from ethanol.

*Anal.* Calcd for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.45; H, 4.94; N, 12.29.

Further elution with benzene–chloroform (1:1) provided pure *trans*-1-methyl-2,5-diphenylpyrrolidine (**5b**) as a colorless oil (0.8 g). Purification by preparative gas chromatography gave an analytical sample.

*Anal.* Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.05; H, 7.86; N, 6.04.

The picrate had mp 175° from ethanol.

*Anal.* Calcd for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.35; H, 5.04; N, 12.08.

**2,4-Diphenylpyrrolidine** was prepared according to Kloetzel by hydrogenation of 4-nitro-1,3-diphenyl-1-butanone,[7] bp 165° (1.5 mm) [lit.[7] bp 182.5° (3.8 mm)]. The product gave a benzamide, mp 122° (lit.[7] mp 122–124°).

**Methylation of 2,4-diphenylpyrrolidine** was carried out according to Icke, *et al.*,[14] using 1.56 g of 2,4-diphenylpyrrolidine, 1.75 ml of formic acid, and 1.60 ml of a 30% solution of formaldehyde. After work-up 1.0 g of product was isolated by distillation, bp 120° (0.5 mm).

*Anal.* Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.25; H, 8.23; N, 5.88.

The nmr spectrum of the product showed the aromatic protons at δ 7.5–7.1 (m, 10 H), the N–Me protons as two singlets in the ratio of approximately 1:3 at 2.25 and 2.18, respectively, and the rest of the protons as multiplets at 3.7–1.6.

**Registry No.**—*cis*-**3**, 1145-91-1; *trans*-**3**, 1145-92-2; **4a**, 22147-83-7; **4b**, 35657-63-7; **4b** picrate, 35657-64-8; **5a**, 22147-84-8; **5b**, 35657-66-0; **5b** picrate, 35657-67-1; 1-methyl-2,4-diphenylpyrrolidine, 35657-68-2.

(9) J. B. Cloke, *J. Amer. Chem. Soc.*, **51**, 1174 (1929).

(10) Rearrangement of the cyclopropyl ketimine to a pyrroline by a concerted mechanism does not seem likely, as no 2,4-diphenylpyrrolidines were found in the product mixture.

(11) For similar reductions of enamines see N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, **79**, 6210 (1957).

(12) In all known examples of this reaction the product resulting from the approach of the reducing agent from the least hindered side predominates: (a) D. G. Hey, G. D. Meakins, and T. L. Whateley, *J. Chem. Soc. C*, 1509 (1967); (b) M. Davis, E. W. Parnell, and D. Warburton, *ibid.*, 1688 (1966); (c) D. S. Noyce and F. W. Bachelor, *J. Amer. Chem. Soc.*, **74**, 4577 (1952); (d) P. F. Coe, B. C. Uff, and J. W. Lewis, *J. Chem. Soc. C*, 2265 (1968); (e) R. R. Sauers, *J. Amer. Chem. Soc.*, **80**, 4721 (1958).

(13) All boiling points and melting points are uncorrected. Nmr spectra were measured by a Jeol C-60H instrument in $CDCl_3$; all chemical shifts are given in parts per million downfield from TMS. All gas chromatographic work was carried out on an F & M Model 720 dual column programmed temperature gas chromatograph on a 6 ft × 0.25 in., 10% diethylene glycol succinate on Chromosorb W column. Microanalyses were carried out by the Hebrew University Microanalytical Laboratory.

(14) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 723.

## Structure and Proton Magnetic Resonance Study of 3-(*N'*-Aziridinyl)succinimides[1a]

P. JOSEPH-NATHAN,* V. MENDOZA, AND E. GARCÍA G.[1b]

*Departamento de Química, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P. O. Box 14-740, México 14, D.F., México.*

*Received May 30, 1972*

In an earlier communication,[2] it was shown that reaction of N-substituted maleimides with ethereal solutions of diazomethane gave instantaneously the corresponding pyrazolines in high yields. Extending further the studies on the reactivity of maleimides, we describe now the results obtained with aziridine.[3]

Mild treatment of N-substituted maleimides with aziridine gave solid adducts whose elemental composition corresponded to the combination of equimolecular amounts of aziridine and of the maleimide.

The adducts showed an infrared absorption band at 1720 $cm^{-1}$ corresponding to the imide carbonyl groups. Their 100-MHz pmr spectra showed, in addition to the signals of the N substituent, the presence of an ABX system ($\delta_A$ 3.01, $\delta_B$ 2.90, and $\delta_X$ 2.59 ppm; $J_{AB}$ = 18, $J_{AX}$ = 7.5, and $J_{BX}$ = 4.5 Hz) attributable to a $-CH_2-CH-$ moiety on a five membered ring. The CH signal is found at higher fields than the AB signals of the methylene group. In the high field region there is a strongly coupled four-proton system, which even at 220 MHz remained complex. It showed signals at 2.036 (1 H), ~1.873 (2 H), and 1.359 (1 H) ppm. In view of these results, and considering that N-substituted

(1) (a) Presented at the VII Congreso Mexicano de Química Pura y Aplicada, Morelia, Mich., México, April 1972. (b) This work is part of the M.S. thesis of E. G. G. who receives a CoNaCyT (México) scholarship (1970–1972).

(2) V. Mendoza, P. Joseph-Nathan, and C. Perez, *Rev. Soc. Quim. Mex.*, **15**, 103 (1971).

(3) O. C. Dermer and G. E. Man, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, Chapter 3.

aziridines provide relatively simple pmr spectra,[4-8] some chemical reactions were done to establish the structure of the adducts.

Treatment of the adduct (IIb), derived from *N*-(*p*-methoxyphenyl)maleimide (Ib), with sodium borohydride gave *N*-(*p*-methoxyphenyl)succinimide which was identified by direct comparison with an authentic sample.[9] Catalytic hydrogenation of IIb gave a compound to which structure IIIa could be ascribed. Its 100-MHz-pmr spectrum showed, in addition to the *p*-methoxyphenyl moiety, and ABX system ($\delta_A$ 2.65, $\delta_B$ 3.00, and $\delta_X$ 3.88 ppm; $J_{AB}$ = 18; $J_{AX}$ = 6, and $J_{BX}$ = 8 Hz) corresponding to the five-membered ring protons, a NH signal at 1.85 ppm which disappeared after equilibration with $D_2O$ and an ethyl group [triplet $J$ = 7 Hz at 1.16 (3 H) ppm and quartet $J$ = 7 Hz at 2.75 (2 H) ppm]. The acetyl derivative (IIIb) showed the absence of the NH signal and the presence of a new singlet (3 H) at 2.15 ppm.

Treatment of the original adduct (IIb) with acetic anhydride gave a compound $C_{17}H_{20}O_6N_2$, which showed ir bands at 1745 (ester carbonyl), 1720 (imide carbonyls), and 1650 $cm^{-1}$ (amide carbonyl). The pmr spectrum is consistent with structure IV (see the Experimental Section).

The above chemical evidence confirms structure IIb. In order to explain the pmr signals, measurements in DMSO-$d_6$ were performed. Most signals still appear as when measured in $CDCl_3$ but the ABX system of the five-membered-ring protons showed now an $AB_2$ system at 3.05 and at 2.80 ppm in which the CH proton is found at lower fields than the methylene signals. Variable temperature measurements (see Figure 1) revealed that near 120° the signals of the high field, strongly coupled, four-proton aziridine system collapsed to a singlet (4 H) at 1.67 ppm. When the sample is cooled down again to room temperature the complex nmr pattern due to the protons of the aziridine ring reappeared. This indicates that at higher temperatures the aziridine ring rotates freely, that its nitrogen lone pair inverts fast in the nmr time scale, or that both phenomena are present since otherwise the protons of the ring would originate $A_4$ or $A_2B_2$ systems.[5,7] At room temperature there should therefore exist a preferred conformation of the three-membered ring in respect to the imide ring. In addition there is no evidence for slow invertion of the lone pair of the aziridine nitrogen which should cause duplicities of the CH signal bearing the three-membered ring.[10] This is not observed even at 220 MHz.

This suggests that an interaction of the lone pair of electrons of the aziridine nitrogen atom with the phenyl ring or with one of the carbonyl groups could exist. In order to obtain more information of this interaction, the adduct of aziridine and *N*-methylmaleimide (Ia) was prepared. The product (IIa) showed again the complex spin–spin pattern in the high field region of the pmr spectrum suggesting that the interaction is due to a carbonyl group and that there is restricted rotation around the C–N band.[10] An alternate less probable explanation could involve the two nitrogen atoms of the molecule. Unfortunately this could not be excluded since reaction of maleic anhydride and aziridine gave only polymeric material. Treatment

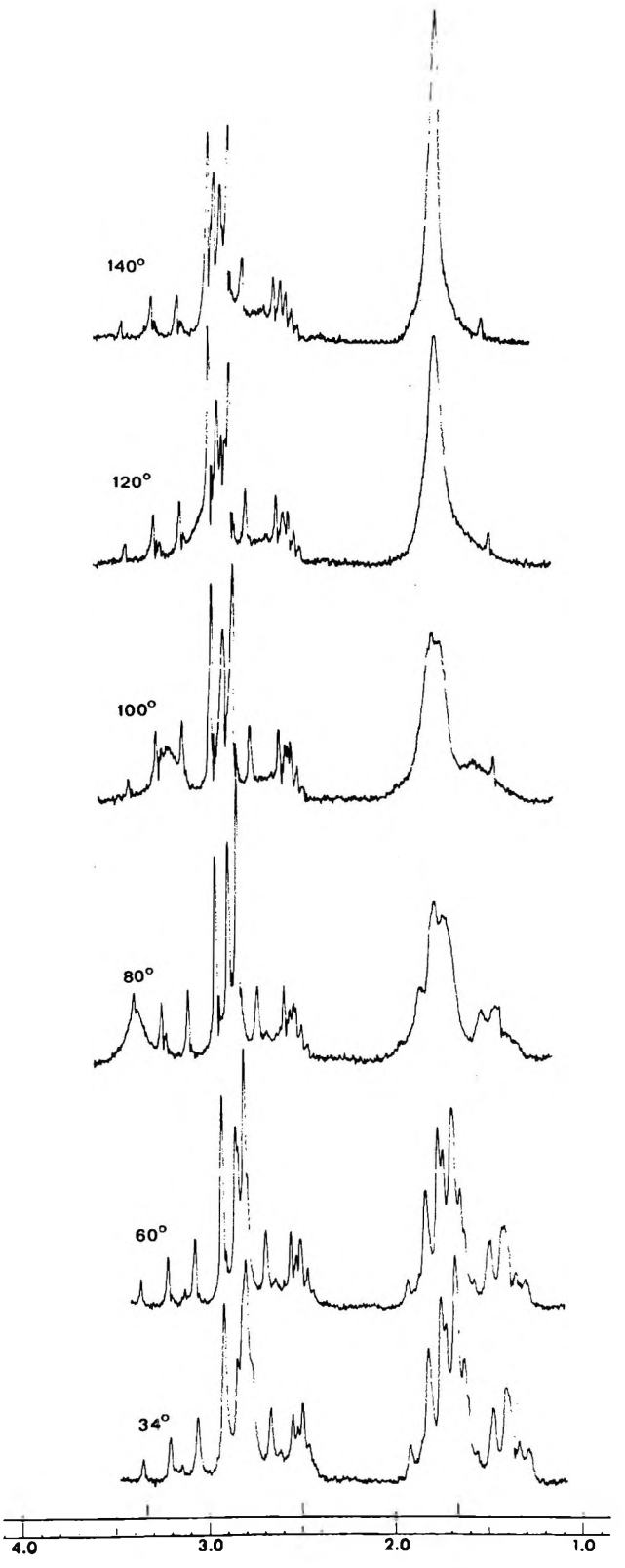
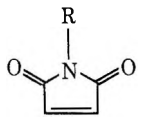


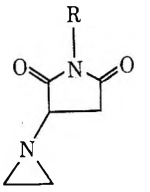

Figure 1.—High field region of the 60-MHz pmr spectra of *N*-(*p*-methoxyphenyl)-3-(*N'*-aziridinyl)succinimide (IIb) in DMSO-$d_6$ at various temperatures.

(4) M. Jautelat and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 642 (1969).
(5) S. J. Brois, *Tetrahedron*, **26**, 227 (1970).
(6) J. D. Andose, J.-M. Lehn, K. Mislow, and J. Wagner, *J. Amer. Chem. Soc.*, **92**, 4050 (1970).
(7) J. T. Rudesill, R. F. Severson, and G. Pomonis, *J. Org. Chem.*, **36**, 3071 (1971).
(8) D. L. Nogel, P. B. Woller, and N. H. Cromwell, *ibid.*, **36**, 3911 (1971).
(9) A. Arcosia, H. Lumbroso, and R. Passerini, *Bull. Soc. Chim. Fr.*, 754 (1959).
(10) D. J. Anderson, D. C. Horwell, and R. S. Atkinson, *J. Chem. Soc. C*, 624 (1971).

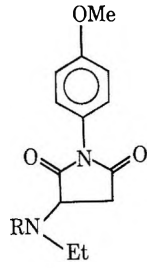
of *N*-(*p*-carbomethoxyphenyl)maleimide (Ic) with aziridine gave the corresponding adduct (IIc) whose pmr spectrum showed the complex high field signals.



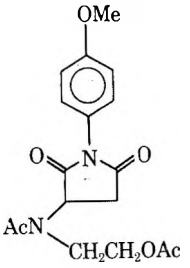
Ia, R = Me
b, R = *p*-MeOC$_6$H$_4$
c, R = *p*-MeOOCC$_6$H$_4$



IIa, R = Me
b, R = *p*-MeOC$_6$H$_4$
c, R = *p*-MeOOCC$_6$H$_4$



IIIa, R = H
b, R = Ac



IV

## Experimental Section

Melting points are uncorrected. Infrared spectra were determined in $CHCl_3$ solutions on a Perkin-Elmer 421 spectrophotometer. Ultraviolet spectra were measured in 95% EtOH solutions using a Unicam SP-800 spectrophotometer. Nuclear magnetic resonance spectra were determined using Varian Associates A-60, HA-100, and HR-220 spectrometers. Variable temperature measurements were performed with the aid of V-6040 variable temperature controllers. Chemical shifts are in ppm relative to internal TMS. The elemental analysis were performed by the Alfred Bernhardt Laboratories, West Germany.

*N*-(*p*-**Methoxyphenyl**)-**3**-(*N'*-**aziridinyl**)**succinimide** (**IIb**).—A solution of 9 g of *N*-(*p*-methoxyphenyl)maleimide (**Ib**) in 250 ml of anhydrous ether and a few drops of pyridine was cooled in an ice bath and treated dropwise under stirring with aziridine, until the yellow solution was completely colorless. A small amount of a pale pink solid that is formed during the reaction was removed by filtration. The solution was washed with water, dried over anhydrous $Na_2SO_4$, and evaporated. Crystallization from ether–hexane gave 7.5 g (69%) of white prisms, mp 103–104°. The analytical sample showed mp 105–106°; $\lambda_{max}$ 218, 240, 271 mμ (ε 3000, 7700, 1500); ir bands at 1720 (carbonyl groups) and 1610 and 1590 cm$^{-1}$ (C=C double bonds).

*Anal.* Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; O, 19.49; N, 11.38. Found: C, 63.56; H, 5.83; O, 19.54; N, 11.25.

*N*-**Methyl**-**3**-(*N'*-**aziridinyl**)**succinimide** (**IIa**).—Treatment of 1 g of *N*-methylmaleimide (Ia) as in the previous case gave 745 mg (54%) of IIa as prisms: mp 60–61°; $\lambda_{max}$ 215, 248, 272 mμ (ε 800, 2200, 500); ir band at 1710 cm$^{-1}$ (carbonyl groups).

*Anal.* Calcd for $C_7H_{10}O_2N_2$: C, 54.54; H, 6.54; O, 20.76; N, 18.17%. Found: C, 54.58; H, 6.63; O, 20.82; N, 18.04%.

*N*-(*p*-**Carbomethoxyphenyl**)-**3**-(*N'*-**aziridinyl**)**succinimide** (**IIc**).—Treatment of 5 g of Ic as in the previous cases gave 4 g (67%) of IIc as prisms: mp 113–114°; $\lambda_{max}$ 218, 246 mμ (ε 2900, 11,200); ir bands at 1725 (carbonyl groups) and 1605 cm$^{-1}$ (C=C double bonds); Rast 284, mol wt 274.

*Anal.* Calcd for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.14; O, 23.33; N, 10.21. Found: C, 61.18; H, 5.25; O, 23.35; N, 10.08.

*N*-(*p*-**Methoxyphenyl**)**succinimide**.—A solution of 300 mg of IIb in 30 ml of tetrahydrofuran was refluxed during 5 hr in the presence of 300 mg of sodium borohydride. The mixture was cooled and filtered and the clear filtrate evaporated to a small volume. Upon addition of hexane, there crystallized 150 mg (60%) of *N*-(*p*-methoxyphenyl)succinimide, mp 151–153°. The analytical sample was obtained as white needles, mp 165–166°. This material was identified by standard procedures with a sample obtained by catalytic hydrogenation of *N*-(*p*-methoxyphenyl)maleimide.[8]

**Catalytic Hydrogenation of IIb**.—A solution of 500 mg of the compound in 80 ml of ethyl acetate was hydrogenated in the presence of 40 mg of prehydrogenated 10% Pd/C catalyst until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solution concentrated to a small volume. Crystallization from ethyl acetate–hexane gave 432 mg (86%) of IIIa as white prisms mp 112–114°. The analytical sample (ether–hexane) showed mp 115–116°; $\lambda_{max}$ 218, 237, 272 mμ (ε 4600, 9900, 2100); ir bands at 3310 (amine), 1710 (carbonyl groups), and 1610 and 1590 cm$^{-1}$ (C=C double bonds).

*Anal.* Calcd for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; O, 19.33; N, 11.28. Found: C, 62.98; H, 6.46; O, 19.39; N, 11.18.

**Acetylation of IIIa**.—Treatment of 300 mg of IIIa with $Ac_2O$–AcONa at room temperature during 12 hr, followed by work-up as usual, gave 197 mg (56%) of IIIb as white prisms: mp 117–118°; $\lambda_{max}$ 218, 245, 272 mμ (ε 2900, 8700, 2600); ir bands at 1720 (imide carbonyls), 1640 (amide carbonyl), and 1610 cm$^{-1}$ (C=C double bands).

*Anal.* Calcd for $C_{15}H_{18}O_4N_2$: C, 62.06; H, 6.25; O, 22.04; N, 9.65. Found: C, 62.17; H, 6.21; O, 22.23; N, 9.64.

**Treatment of IIb with Acetic Anhydride**.—A sample of 500 mg of IIb was treated with $Ac_2O$–AcONa as described above. Crystallization from ether–hexane gave 335 mg (47%) of IV as white prisms: mp 136–137°; $\lambda_{max}$ 218, 236, 272 mμ (ε 4700, 8900, 1600); ir bands at 1745 (ester carbonyl), 1720 (imide carbonyls), 1650 (amide carbonyl), and 1610 and 1590 cm$^{-1}$ (C=C double bonds); nmr methoxyl at 3.82 (s), acetyls at 2.15 (s) and 2.08 (s), aromatics at 7.20 (2 H) and 7.01 (2 H), $NCH_2CH_2O$ at 4.22 (2 H) and 3.75 (2 H), and ring protons at 4.07 (1 H) and 3.00 (2 H) ppm.

*Anal.* Calcd for $C_{17}H_{20}O_6N_2$: C, 58.61; H, 5.79; O, 27.56; N, 8.04. Found: C, 58.56; H, 5.92; O, 27.48; N, 8.12.

**Registry No.**—IIa, 35740-37-5; IIb, 35740-75-1; IIc, 35740-76-2; IIIa, 35740-77-3; IIIb, 35740-78-4; IV, 35740-79-5.

**Acknowledgment.**—We are grateful to Professor K. C. Tsou (School of Medicine, University of Pennsylvania), Dr. M. Cohn, and Miss Karen Norton for the 220-MHz measurements, which were done using the facilities provided by NIH Research Grant No. 1 P07 RR-00542-01 from the Division of Research Facilities and Resources.

---

# The Mechanism of Formation of Benzo[*g*]quinolones *via* the Combes Reaction

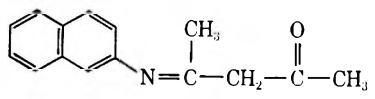
JERRY L. BORN

*Department of Medicinal Chemistry, College of Pharmacy, Butler University, Indianapolis, Indiana 46208*

*Received March 7, 1972*

Treatment of the condensation products of 2-aminonapthalene and 1,3-dicarbonyl compounds with $H_2SO_4$ provides a convenient method of synthesis of benzo[*g*]quinolines.[1-3] The formation of benzo[*g*]quinolines rather than the expected benzo[*f*]quinolines has been explained in two ways: Johnson[2] has proposed that the anil 1 affords linear products because of a larger deactivation of the one position with respect to the three position in the naphthalene ring; Huigsen[3]

(1) W. S. Johnson and F. J. Mathews, *J. Amer. Chem. Soc.*, **66**, 210 (1944).
(2) W. S. Johnson, E. Woroch, and F. J. Mathews, *ibid.*, **69**, 566 (1947).
(3) R. Huisgen, *Justus Liebigs Ann. Chem.*, **564**, 16 (1949).



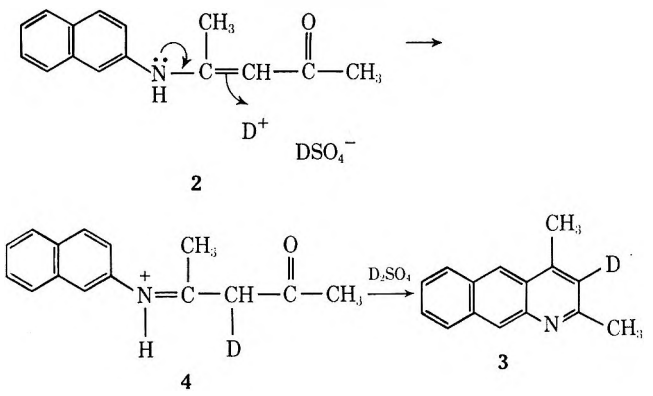
1

has proposed that the enamine **2** is protonated at the one position of the aromatic ring to block the formation of angular products.

The structure of the condensation product of acetylacetone and 2-aminonaphthalene is the enamine **2** as indicated by Huisgen's isolation of 2-acetylaminonaphthalene from the permanganate oxidation of **2**, the nmr spectra of **2**, and the comparison of the uv spectra of **2** with those of other known enamines of the same general structure. The treatment of **2** with $D_2SO_4$ produced 3-deuterio-2,4-dimethylbenzo[*g*]quinoline (**3**) which was identical except for the $H_3$ signal with a sample prepared with $H_2SO_4$. The assignment of the chemical shifts of protons $H_3$ (δ 6.94), $H_5$ (8.43), and $H_{10}$ (8.60) is based on electron densities reported for benzo[*g*]quinoline[4,5] and the accepted assignment of chemical shifts in various quinolines.

The lack of incorporation of deuterium into the 10 position of **3** clearly indicates that Huisgen's proposed mechanism is not correct. The formation of **3** most likely proceeds by the mechanism shown in Scheme I. The protonation of **2** to give **4** lends credence to

SCHEME I



Johnson's rationalization of the formation of benzo [*g*]-quinolines *via* the Combes reaction.

### Experimental Section[6]

**2-(2-Naphthyl)amino-2-penten-4-one** (**2**).—2-Aminonaphthalene and acetylacetone were condensed as described by Johnson:[1] mp 99° (lit. mp 99°); nmr δ ($CDCl_3$) 2.04 (s, 6 H), 5.1 (s, 1 H), 7.45 (m, 7 H), 12.7 (b s, 1 H); $\lambda_{max}^{i\text{-PrOH}}$ 337 nm (ε 23,000).

**2,4-Dimethylbenzo[*g*]quinoline.**—The enamine **2** was treated with $H_2SO_4$ as described by Johnson:[1] mp 92° (lit. mp 93°); nmr δ ($CDCl_3$) 2.62 (s, 3 H), 2.67 (s, 3 H), 6.94 (s, 1 H), 7.43 (m, 2 H), 7.95 (m, 2 H), 8.31 (s, 1 H), 8.56 (s, 1 H).

**3-Deuterio-2,4-dimethylbenzo[*g*]quinoline** (**3**).—**2** (1 g, 0.044 mol) was treated with 3 g of $D_2SO_4$ as described by Johnson.[1] The crude material was dried and chromatographed on Brinkman silica gel, eluting with $CHCl_3$. The material so obtained was recrystallized from petroleum ether to give 52% **3**: mp 92° (lit. mp 93°); nmr δ ($CDCl_3$) 2.58 (s, 3 H), 2.65 (s, 3 H), 7.44 (m, 2 H), 7.96 (m, 2 H), 8.31 (s, 1 H), 8.56 (s, 1 H).

**Registry No.**—**3**, 35666-88-7.

(4) M. J. S. Dewar and G. J. Glecher, *J. Chem. Phys.*, **44**, 759 (1966).
(5) K. Nishimoto and L. S. Foster, *Theor. Chim. Acta*, **4**, 155 (1966).
(6) Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were obtained with a Perkin-Elmer R-12A spectrometer and are reported relative to TMS. Uv spectra were recorded using a Perkin-Elmer-Coleman 124 spectrophotometer.

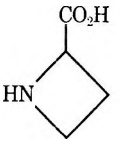
## The Synthesis of Azetidine-3-carboxylic Acid[1,2]

ARTHUR G. ANDERSON, JR.,* AND ROGER LOK

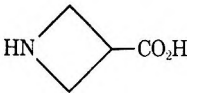
*Department of Chemistry, University of Washington, Seattle, Washington 98195*

*Received June 8, 1972*

L-Azetidine-2-carboxylic acid (**1**) occurs in nature.[3] It has been shown to inhibit the growth of *E. coli* cultures and various seedlings[4] and to cause abnormalities in growing embryos.[5] The X-ray structure showed the ring to be 11° out of plane and it was postulated that the incorporation of **1** in a polypeptide chain could cause the direction of successive amide bonds in the α helix of the peptide tertiary structure to change by 16°.[6] As an extension of studies on azetidines,[7] it was therefore of interest to synthesize the isomeric azetidine-3-carboxylic acid (**2**).

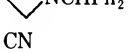


**1**



**2**

Chatterjee and Triggle[8] had reported the preparation of the hydrochloride of 1-benzhydrylazetidin-3-ol (**3**) from epichlorhydrin and benzhydrylamine, but gave no experimental details or yields. Application of the procedure described by Gaertner[9] to this reaction gave 60–65% yields of the salt of **3**. Tosylation of **3** gave only 39% of the corresponding ester **4**, and reaction with

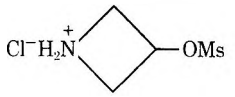
**3**, X = OH
**4**, X = OTs
**5**, X = OMs
**6**, X = OMe
**7**, X = OEt
**8**, X = Br
**9**, X = 
**10**, X = CN
**11**, X = $CO_2H$
**12**, X = $CH_2NH_2$

(1) Presented in part at the 25th Annual Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 1970, Organic Chemistry Abstracts, No. 131, 1970, p 74.
(2) From the Ph.D. thesis of Roger Lok, University of Washington, 1971. Supported in part by the Graduate Research Fund, University of Washington.
(3) L. Fowden, *Biochem. J.*, **64**, 323 (1956); L. Fowden, *Advan. Enzymol.*, **29**, 89 (1967).
(4) L. Fowden and M. H. Richard, *Biochem. Biophys. Acta*, **71**, 459 (1963); E. J. Hewitt and B. A. Notton, *Phytochemistry*, **6**, 1329 (1967).
(5) D. J. Cummings, V. A. Chapman, S. S. Delong, and L. Mondale, *J. Virol.*, **1**, 193 (1967).
(6) H. M. Berman, E. L. McCandy, J. W. Burgner, II, and R. L. Van Etten, *J. Amer. Chem. Soc.*, **91**, 6177 (1969).
(7) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 3046 (1968), and references cited therein.
(8) S. S. Chatterjee and D. J. Triggle, *Chem. Commun.*, 93 (1968).
(9) V. R. Gaertner, *Tetrahedron Lett.*, 4691 (1966).

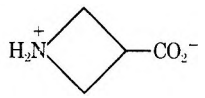
chlorosulfonic acid afforded only a moderate yield (50%) of impure sulfate ester, but the mesylate derivative **5** formed in high yield.

It was noted that loss of material occurred when **4** was recrystallized from hot methanol, and the supposition that this was due to alcoholysis was confirmed when heating **4** and methanol under reflux gave 51% of the methyl ether **6**. Analogously, treatment of **5** with ethanol or sodium bromide formed **7** (37%) and **8** (85%), respectively. It was envisioned that carboxylation of the Grignard reagent of **8** followed by hydrogenolysis of the benzhydryl group would give **2**, but the Grignard reaction gave a low yield of dimeric product **9** and unchanged **8**. Reaction of **5** with sodium cyanide afforded 75% of the nitrile **10** and hydrolysis of this gave the carboxylic acid **11** in 75–86% yield.

It remained to remove the benzhydryl group by hydrogenolysis. An attempt to effect this operation at an earlier stage (on the hydrochloride of **5**) using 5% Pd/C in methanol gave unchanged starting material. Pearlman[10] has reported the debenzylation of amines catalyzed by palladium hydroxide on carbon, and this method gave **13** in nearly quantitative yield.[11] Application of this procedure to **11** gave **2** in essentially




**13**

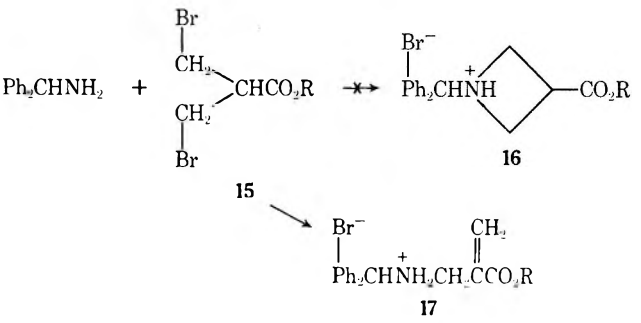



**14**

quantitative yield. It was found, in contrast, that under these conditions the hydrochloride of **10** underwent selective reduction of the cyano group to give a low yield of a product identified by its pmr and mass spectra as **12**. Subsequently **12** was also obtained from the lithium aluminum hydride reduction of **10**.

The $pK_a$ values of **2** (3.2 ± 0.1 and 10.3 ± 0.1) were similar to those of β-proline. An X-ray structural analysis of crystalline **2** showed it to exist as the dipolar ion **14** and that the ring was puckered by less than 1°.[12] This new amino acid is undergoing testing for biological activity.

An alternative route to **2** was investigated based on the finding by Cromwell and coworkers[13] that treatment of 1-*tert*-butylamino-2-benzoyl-3-bromo-3-phenylpropane with *tert*-butylamine effected cyclization to the azetidine. In the proposed sequence benzhydrylamine would participate in a double displacement on the dibromo ester **15** to form **16**. Esters with the structure of **15** having R = ethyl and benzyl were prepared from the corresponding acid,[14] but reaction of these with benzhydrylamine gave only monodisplacement, monoelimination products (**17**).




**15** **16**




**17**

### Experimental Section

All pmr spectra were recorded on Varian A-60 or T-60 spectrometers and are reported in parts per million (τ) relative to internal TMS. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer with the assistance of George Tsou, Peter Wade, and William Howald and with perfluorotributylamine (70 eV) as the reference standard. $pK_a$ values were determined with an automatic titrator Radiometer, type TTTlc. Melting points and boiling points are uncorrected. Elemental analyses were performed by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany, and Chemalytics, Inc., Temple, Ariz. Organic solutions were dried over $MgSO_4$. Solvents were reagent grade. THF and ether were dried by distillation from $LiAlH_4$. Pyridine was distilled from BaO. Pentane was distilled from concentrated sulfuric acid. DMF was distilled from BaO. Hydrochloride salts of amines were prepared by passing dry HCl into an ethereal solution of the amine.

**1-Benzhydrylazetidin-3-ol** (**3**).—A mixture of 46.3 g (0.5 mol) of epichlorohydrin, 91.6 g (0.5 mol) of benzhydrylamine, and 200 ml of methanol was allowed to stand protected from light for 3 days and then refluxed for 3 days.[9] The methanol was removed (reduced pressure) and the residue was washed with acetone. The residue from the washes was refluxed with methanol and the solvent was then removed. The combined solids (85–90 g) were partitioned between ether and 6 *N* NaOH and removal of the solvent from the dried ethereal solution gave 75 g (61%) of **3** as a colorless solid, mp 107–110°. A sample sublimed at 80° (1 mm) had mp 113° (lit.[8] mp 115°); ir ($CHCl_3$) 3640 $cm^{-1}$ (OH); pmr ($CDCl_3$) τ 7.13 (t, 2, $J$ = 7 Hz, CHNCH), 6.55 (t, 2, $J$ = 7 Hz, CHNCH), 6.02 (s, 1, OH), 5.7 (s, 1, $Ph_2CH$), 5.66 (m, 1, CHOH), and 2.75 (m, 10, ArH).

*Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.31; H, 7.16; N, 5.85. Found: C, 80.50; N, 7.03; N, 6.02.

**1-Benzhydryl-3-*p*-toluenesulfonatoazetidine** (**4**).—To 2.51 g (10.5 mmol) of **3** in 15 ml of dry pyridine was added 2 g (10.5 mmol) of *p*-toluenesulfonyl chloride at −10° with stirring. The mixture was kept cold for 1.5 hr and then poured into an ice–water mixture. The oil which formed was separated. It solidified on standing (refrigerator) and amounted to 1.6 g (39%) of **4**, mp 101–104°. Extraction of the pyridine solution (saturated with $K_2CO_3$) with ether gave 1 g of unchanged **3**. A sample of **4** after recrystallization from methanol had mp 106–107°; ir ($CHCl_3$) 1360 $cm^{-1}$ (SO); pmr ($CCl_4$) τ 7.74 (s, 3, $ArCH_3$), 7.02 (t, 2, $J$ = 7 Hz, CHNCH), 6.65 (t, 2, $J$ = 7 Hz,CHNCH), 5.75 (s, 1, $Ph_2CH$), 5.21 (p, 1, $J$ = 6 Hz, CHOTs), and 2.35–2.81 (m, 14, ArH).

*Anal.* Calcd for $C_{23}H_{23}NO_3S$: C, 70.21; H, 5.85; N, 3.56; S, 8.14. Found: C, 70.06; H, 5.82; N, 3.37; S, 8.21.

**1-Benzhydryl-3-methanesulfonatoazetidine** (**5**).—To a solution of 71.7 g (0.3 mol) of **3** in 600 ml of anhydrous pyridine maintained at −20° was added slowly with stirring 51.75 g (0.45 mol) of methanesulfonyl chloride. Stirring was continued for 1 hr and the mixture, protected from moisture, was allowed to stand in a refrigerator overnight. The mixture was then poured into ice and $H_2O$. The collected, dried precipitate of crude **5** amounted to 104.3 g (110%),[15] mp 100–110°. A sample purified by extraction with *n*-pentane (Soxhlet) was obtained as colorless crystals: mp 113–114°; ir ($CS_2$) 1360 and 1180 $cm^{-1}$ (SO); pmr ($DCCl_3$) τ 7.23 (s, 3, $SCH_3$), 6.45 (t, 2, $J$ = 7.5 Hz, CHNCH), 6.88 (t, 2, $J$ = 7.5 Hz, CHNCH), 5.63 (s, 1, $Ph_2CH$), 4.97 (p, 1, $J$ = 6 Hz, CHOMs), and 2.69 (m, 10, ArH).

*Anal.* Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.43; S, 10.1. Found: C, 64.19; H, 5.82; N, 4.60; S, 9.97.

**1-Benzhydryl-3-methoxyazetidine** (**6**).—A mixture of 0.317 g (0.76 mmol) of **4**, 2 ml of anhydrous methanol, and 0.2 g of anhydrous sodium carbonate was refluxed for 4 hr and then filtered. The residue from the filtrate was partitioned between

(10) W. M. Pearlman, *Tetrahedron Lett.*, 1663 (1967).

(11) N. H. Cromwell and R. M. Rodebaugh, *J. Heterocycl. Chem.*, **6**, 435 (1969), had found this catalyst to be superior to the usual Pd/C for an analogous reaction in the synthesis of azetidine-2-carboxylic acid.

(12) Performed by S. Smith. The details will be published separately.

(13) N. H. Cromwell, J. L. Imbach, E. Doomes, and R. P. Rebman, *J. Org. Chem.*, **32**, 78 (1967).

(14) A. F. Ferris, *ibid.*, **20**, 780 (1955).

(15) Yields of crude **5** ranged from 90 to *ca.* 100% for eight runs.

$HCCl_3$ and aqueous sodium carbonate. The residue of crude **6**, mp 50–53°, obtained from the separated, dried organic layer amounted to 0.1 g (51%). A sample purified by sublimation at 50° (0.05 mm) had mp 55–57°; pmr ($CCl_4$) 7.2 (t, 2, $J$ = 6.5 Hz, CHNCH), 6.9 (s, 3, $OCH_3$), 6.58 (t, 2, $J$ = 6.5 Hz, CHNCH), 6.1 (p, 1, $J$ = 6 Hz, CHOMe), and 2.77 (m, 10, ArH).

*Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.47; H, 7.69; N, 5.39.

**1-Benzhydryl-3-ethoxyazetidine (7).**—From 0.317 g (1 mmol) of **5**, 2 ml of absolute methanol, and 0.2 g of anhydrous sodium carbonate treated as described for the preparation of **6** was obtained 0.1 g (37%) of **7**, mp 65–67°, after sublimation of the crude product at 60° (1 mm): pmr ($CCl_4$) 8.93 (t, 3, $J$ = 7.5 Hz, $CH_2CH_3$), 7.22 (t, 2, $J$ = 7 Hz, CHNCH), 6.73 (q, 2, $J$ = 7.5 Hz, $CH_2CH_3$), 6.58 (t, 2, $J$ = 7 Hz, CHNCH), 6.0 (p, 1, $J$ = 6 Hz, CHOEt), 5.73 (s, 1, $Ph_2CH$), and 2.75 (m, 10, ArH); molecular ion at $m/e$ 267.259 (calcd for $C_{11}H_{21}NO$: 267.1623).

**1-Benzhydryl-3-bromoazetidine (8).**—1-Benzhydryl-3-methanesulfonatoazetidine (**5**) (12.7 g, 40 mmol) was added to a solution of 6.2 g (60 mmol) of NaBr in 80 ml of diethylene glycol. The mixture was heated at 60–65° for 2.5 hr, cooled to room temperature, and extracted with $CCl_4$. Removal of the solvent from the combined washed ($H_2O$) and dried extracts left 10.3 g (85%) of **8**, mp 95–99°. A sample recrystallized from ethanol had mp 101–102°; pmr ($CCl_4$) 6.65 (t, 2, $J$ = 7 Hz, CHNCH), 6.31 (t, 2, $J$ = 7 Hz, CHNCH), 5.65 (m, 1, CHBr), 5.61 (s, 1, $Ph_2CH$), and 2.67 (10, m, ArH).

*Anal.* Calcd for $C_{16}H_{16}NBr$: C, 63.59; H, 5.34; Br, 26.44; N, 4.65. Found: C, 63.71; H, 5.47; Br, 26.43; N, 4.77.

**3,3′-Bis-1-benzhydrylazetidine (9).**—A solution of 3.02 g (10 mmol) of **8** in 30 ml of dry ether was stirred under reflux with 0.243 g (10 g-atoms) of Mg turnings until the Mg disappeared (10 hr). Stirring was continued while gaseous $CO_2$ was passed over the solution for 2 hr. The mixture was poured onto crushed, solid $CO_2$ and the whole was extracted with $H_2O$. No precipitate formed when the separated aqueous phase was brought to pH 5 with 6 *N* hydrochloric acid. Removal of the solvent from the dried ether layer and chromatography [tlc on silica gel with 4:1 petroleum ether (bp 30–60°)–ether] of the residue gave unchanged **8** ($R_f$ 0.9) and a small amount of **9** ($R_f$ 0.75): mp 176°; pmr ($CDCl_3$) $\tau$ 7.28 (m, 6, 2 CHNCHCH), 6.84 (m, 4, 2 CHNCH), 5.76 (s, 2, 2 $Ph_2CH$), and 2.73 (m, 20, 2 ArH); molecular ion at $m/e$ 444.257 (calcd 444.2565).

*Anal.* Calcd for $C_{32}H_{32}N_2$: C, 86.44; H, 7.26; N, 6.30. Found: C, 86.26; H, 7.38; N, 6.34.

**1-Benzhydryl-3-cyanoazetidine (10).**—To a solution of 95.1 g (0.3 mol) of **5** in 600 ml of DMF was added a solution of 44.1 g (0.9 mol) of NaCN in 75 ml of $H_2O$. The mixture was heated at 65° with stirring for 24 hr, cooled, and poured into an ice–water mixture. The precipitate was collected and dissolved in 400 ml of dichloromethane. Filtration of the dried organic solution through tlc grade silica gel removed colored impurities. Evaporation of the solvent gave 55.3 g (75%) of **10**: mp 152–153°; ir ($HCCl_3$) 2260 $cm^{-1}$ (C≡N); pmr ($CCl_4$) $\tau$ 6.75 (m, 5, $CH_2CHCH_2$), 5.7 (s, 1, $Ph_2CH$), and 2.7 (m, 10, ArH).

*Anal.* Calcd for $C_{17}H_{16}N_2$: C, 82.23; H, 6.45; N, 11.25. Found: C, 82.16; H, 6.41; N, 11.45.

**1-Benzhydrylazetidine-3-carboxylic Acid (11).**—Solutions of 9.9 g (40 mmol) of **10** in 100 ml of monoethoxyethanol and 8.08 g (144 mmol) of KOH in 6 ml of $H_2O$ were combined and heated at 90–95° for 24 hr, at which time $NH_3$ evolution had ceased. The cooled solution was poured into an ice–water mixture and the whole was acidified (*ca.* pH 5) with 6 *N* hydrochloric acid. The precipitate after collection and drying amounted to 9.2 g (86%) of **11**, mp 180–190°. A sample after sublimation at 80° ($10^{-3}$ mm) had mp 198°; ir (KBr) 1670 and 1370 $cm^{-1}$ (C=O); pmr (DMSO-$d_6$) $\tau$ 6.7 (m, 5, $CH_2CHCH_2$), 5.54 (s, 1, $Ph_2CH$), 4.2 (broad s, 1, $^+NH$), and 2.64 (m, 10, ArH).

*Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.36; N, 5.24. Found: C, 76.34; H, 6.56; N, 5.36.

**Reduction of 1-Benzhydryl-3-cyanoazetidine (10). A. Catalytic.**—A mixture of the hydrochloride of **10** (2.85 g, 10 mmol) dissolved in 200 ml of dry methanol and 0.32 g of $Pd(OH)_2 \cdot C^{10}$ was treated with $H_2$ at room temperature and *ca.* 60 psi until about 0.01 mol of $H_2$ was taken up. The mixture was filtered, the solvent was evaporated from the filtrate, and the residue was extracted with dry THF. Examination (pmr, tlc) of the residue (1.5 g) from the THF extract indicated it to contain **10** plus a small amount of diphenylmethane. The insoluble residue (1.5 g) was partitioned between 6 *N* NaOH and $HCCl_3$. The spectra of the solid obtained from the dried organic layer indicated it to be impure **12**: ir ($CHCl_3$) 3300 $cm^{-1}$ (NH); pmr ($CDCl_3$) $\tau$ 8.83 (s, 2, $NH_2$), 7.58 (m, 1, $CHCH_2N$), 7.23 [m, 4, $(CH)_2CCH_2N$], 6.8 (t, 3, $J$ = 7 Hz, CHCCH), 5.77 (s, 1, $Ph_2CH$), 2.77 (m, 10, ArH); pmr [$CDCl_3$, *ca.* 0.05 *M* Eu(fod)$_3$][16] 7.03 (m, 1, $CHCH_2N$), 6.8 (t, 2, $J$ = 7 Hz, CHCCH), 6.5 (t, 2, $J$ = 7 Hz, CHCCH), 6.13 (d, 2, $J$ = 7 Hz, $CHCH_2N$), 5.57 (s, 1, $Ph_2CH$), 4.37 (s, 2, $NH_2$), and 2.67 (m, 10, ArH); molecular ion at $m/e$ 251.158 [calcd for $C_{17}H_{19}N_2$ (M − 1), 251.1548].

**B. With Lithium Aluminum Hydride.**—A solution of 2.48 g (10 mmol) of **10** in 30 ml of dry THF was added slowly to a suspension of 1.4 g (35 mmol) of lithium aluminum hydride in 10 ml of dry THF and the mixture was stirred overnight and then refluxed for 3 hr. Excess hydride reagent was hydrolyzed by the careful addition, with cooling, of saturated aqueous ammonium chloride, the gelatinous mixture was filtered and the filter cake was washed repeatedly with THF. Evaporation of the solvent from the combined, washed (saturated aqueous NaCl), and dried filtrates left a viscous, yellow oil which gave, after molecular distillation (*ca.* 0.01 mm), 1.79 g (72%) of material identical (ir, pmr and tlc) with the product from **A**.

**3-Methanesulfonatoazetidinium Chloride (13).**—A solution of the hydrochloride salt (3.54 g, 10 mmol) of the mesylate derivative **5** in 75 ml of absolute methanol was treated with $H_2$ in the presence of 0.32 g of $Pd(OH)_2 \cdot C^{10}$ at 50 psi until $H_2$ uptake ceased (1 hr). The mixture was filtered, the solvent was evaporated from the filtrate, and the solid residue was extracted with benzene. From the benzene extract was obtained 1.69 g of diphenylmethane. The residual solid was washed with dichloromethane and then amounted to 1.94 g (104%) of impure **13**, mp 99–101°. A sample after recrystallization from absolute ethanol had mp 104–105°; pmr ($D_2O$) $\tau$ 7.20 (s, 3, $SCH_3$), 5.97 (m, 6, $H_2O$, $H_2CNCH_2$), 4.97 (p, 1, $J$ = 6 Hz, CHOMs).

*Anal.* Calcd for $C_4H_{10}NO_3ClS$: 3, 25.61; H, 5.34; Cl, 18.95; N, 7.46; S, 17.07. Found: C, 25.43; H, 5.43; Cl, 18.80; N, 7.60; S, 16.98.

**Azetidine-3-carboxylic Acid (2).**—A solution of 1 g (3.74 mmol) of the *N*-benzhydryl acid **11** in 200 ml of absolute methanol was treated with $H_2$ for 2 hr as described for the preparation of **13**. The initial solid residue was washed with ether and then amounted to 0.37 g (99%) of **2**. Paper (Whatman No. 3) chromatography (12:3:5 butanol–acetic acid–$H_2O$) gave a spot at $R_f$ 0.32[17] which became purple when sprayed with ninhydrin. The material gave an intense blue color with Feigl's test for imino compounds. Electrophoresis showed migration toward the positive electrode. A sample recrystallized from 90% ethanol had mp 230–275° dec: ir (KBr) 2700–2400 ($^+NH_2$), 1620–1550, and 1400 $cm^{-1}$ ($CO_2^-$); pmr ($H_2O$) $\tau$ 6.47 (m, 1, $CH_2CHCH_2$), 5.87 (d, 4, $J$ = 7 Hz, $CH_2CCH_2$), and 5.3 (s, 2, $H_2O$); mass spectrum $m/e$ 101.0477 (calcd 101.0477); $pK_a^1$ = 3.2 ± 0.1 and $pK_a^2$ = 10.3 ± 0.1.

*Anal.* Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.93; N, 13.87. Found: C, 47.42; H, 6.94; N, 13.85.

**Registry No.**—**2**, 36476-78-5; **3**, 18621-17-5; **4**, 36476-80-9; **5**, 33301-41-6; **6**, 36476-82-1; **7**, 36476-83-2; **8**, 36476-84-3; **9**, 36476-85-4; **10**, 36476-86-5; **11**, 36476-87-6; **12**, 36476-88-7; **13**, 36476-89-8.

(16) Norell Chemical Co., Inc.

(17) The $R_f$ values for proline and azetidine-2-carboxylic acid are 0.39 and 0.35, respectively, under these conditions.

## Synthesis of 2-Benzazepine-1,3-diones and Corresponding 4,5-Dihydro Compounds

GORDON N. WALKER

*Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901*

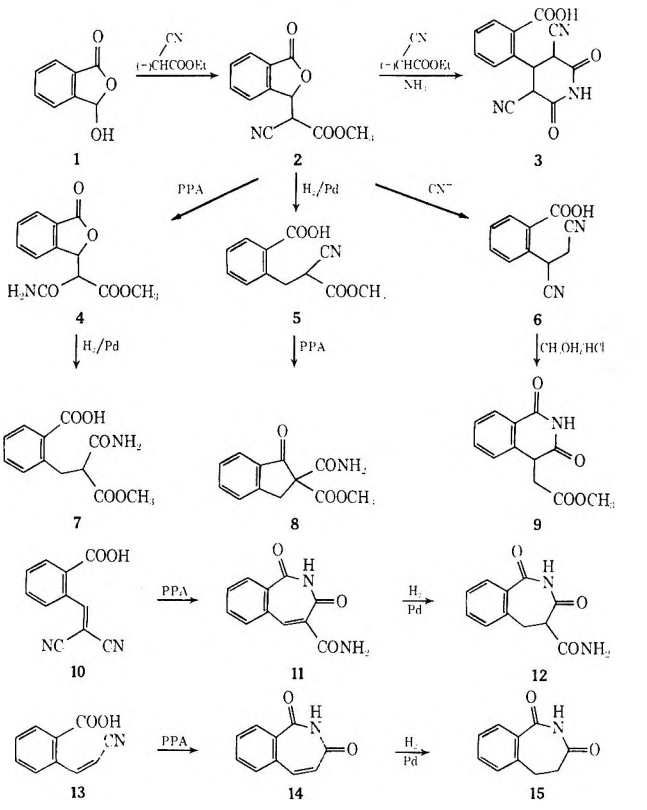
*Received June 9, 1972*

Earlier we reported on the PPA closure of α′-cyano-*trans*-stilbene-*o*-carboxylic acids and *o*-(2-cyano-2-phenylethyl)benzoic acids to 4-aryl-2-benzazepine-1,3-di-

ones and corresponding 4,5-dihydro-4-aryl-2-benzazepine-1,3-diones, respectively.[1] Syntheses of parent substances lacking the 4-aryl groups by a similar approach were also sought, and are now reported.

Consensation of the masked aldehyde group of phthalaldehydic acid (1)[2] (Scheme I) with reactive

SCHEME I



methylene group containing compounds[3] is quite facile in comparison with, *e.g.*, parallel reactions of *o*-benzoylbenzoic acid.[4] Reaction of **1** with ethyl cyanoacetate is even more rapid than that with phenylacetonitrile,[1] and the anion first formed may readily undergo further reactions with nucleophiles. Thus when an additional mole of ethyl cyanoacetate was added and the reaction solution was treated with $NH_3$, the Guareschi imide **3** was obtained.[5] Addition of (aqueous) cyanide after the initial reaction with ethyl cyanoacetate gave dinitrile **6**, which was characterized by conversion to the corresponding triacid and to homophthalimide ester **9**.

Acidification of a water solution of the sodium salt resulting from reaction of **1** with 1 equiv of sodio ethyl cyanoacetate gave nitrile ester lactone **2**. Attempts to obtain the carbomethoxy cinnamonitrile-*o*-carboxylic acid from the rather sensitive compound **2** by acid hydrolyses were unpromising. Treatment of **2** with PPA resulted merely in conversion of the nitrile group to the corresponding amide, **4**. The lactone moiety in this instance thus will not serve in the same capacity as an *o*-COOH group to attack the CN and produce an imide.[1] Alternatively, we investigated the possibility of PPA closure of hydrocinnamonitrile or amide *o*-carboxylic acids derived by ring opening of the lactones. Hydrogenolysis of **2** and **4** in the presence of Pd/C under mild conditions[6] did indeed give the benzoic acids **5** and **7**, respectively. However, no cyclic imides could be obtained by action of PPA on these compounds. The reason was apparent when it was ascertained that the PPA cyclization product from **5** was indanone **8**, acylation of the reactive methine rather than attack on the nitrile moiety having occurred, as in similar closure of benzoic acid 2-thioacetamides with $Ac_2O$–base to thianaphthenones.[7]

A crude, bicarbonate-soluble substance, which appeared to be mainly **10**, was prepared by condensation of **1** with 1 equiv of sodio malononitrile in methanol under mild conditions (as in **1** → **2**). PPA cyclization of the crude condensation product was more rapid than closures of other cinnamonitrile-*o*-carboxylic acids,[1] and from the bicarbonate-insoluble fraction of crude product there was isolated 2-benzazepine-1,3-dione-4-carboxamide (**11**) in low yield. Spectra agreed with structure **11**, and further confirmation was obtained by Pd hydrogenation of **11** to **12**, as in similar hydrogenation of the 4,5 double bond in our earlier 4-aryl analogs of **11**.[1]

To achieve a synthesis of 2-benzazepine-1,3-dione (**14**) itself, which appears to have been approached closely[8] but to date not reported specifically, hydrolysis and decarboxylation of **11** or **12** would not serve, and it was necessary to prepare *cis*-cinnamonitrile-*o*-carboxylic acid (**13**) by the reported inverse Beckmann rearrangement of β-nitroso-α-naphthol.[9] Treatment of **13** with PPA gave **14**, which interestingly showed long-range nmr coupling of vinyl proton 4 to imide proton 2 (see Experimental Section), and finally Pd hydrogenation of **14** afforded **15**.

### Experimental Section[10]

**Methyl α-(3-Phthalidyl)cyanoacetate (2).**—To a solution of 9.3 g (0.405 g-atom) of Na in methanol (500 ml) was added 47 g (0.415 mol) of ethyl cyanoacetate (noticeably endothermic reaction), and 5 min thereafter 60 g (0.40 mol) of phthalaldehydic acid was added. The solution was warmed on a steam cone for 10 min, allowed to stand 0.5 hr while cooling slowly, and reheated on a steam cone for *ca.* 5 min. On standing the solution deposited a sodium salt in quantity. An aqueous solution of this salt was acidified (cooling) weakly with dilute HCl, and the product was collected, washed with water, pressed dry, and triturated with methanol to give 80 g (86%) of crystals, mp 132–134°. Recrystallization from methanol gave a pure sample: mp 140–141°; ir 4.44 (very weak) and 5.67–5.71 μ (doublet); uv 222 nm (ε 11,870) and 290 (9440) with inflection at 281 (9260).

*Anal.* Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.01; H, 3.82; N, 5.88.

**Guareschi Imide (3).**—To a solution of 2.6 g of Na in methanol was added 12 g of ethyl cyanoacetate and then 16.8 g of phthalal-

(1) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).
(2) D. D. Wheeler, D. C. Young, and D. S. Erley, *ibid.*, **22**, 547 (1957).
(3) *Cf.* R. C. Elderfield, *Heterocycl. Compounds*, **2**, 68 (1951).
(4) C. F. Koelsch, *J. Org. Chem.*, **25**, 642 (1960).
(5) I. Guareschi, *Gazz. Chim. Ital.*, **49**, 124 (1919); S. M. McElvain and D. H. Clemens, *J. Amer. Chem. Soc.*, **80**, 3915 (1958).
(6) G. N. Walker and R. J. Kempton, *J. Org. Chem.*, **36**, 1413 (1971).
(7) E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 81 (1948).
(8) G. Simchen, *Angew. Chem.*, **80**, 484 (1968).
(9) J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc. C*, 2059 (1967), and discussion of earlier work therein.
(10) Melting points were obtained using a Thomas-Hoover silicone oil bath; ir spectra (Nujol mulls for solids, films or $CHCl_3$ solutions for oils) were taken on a Perkin-Elmer 21 double beam instrument; uv curves (MeOH solutions) were measured with a Cary 14 recording spectrophotometer; nmr spectra were obtained using a Varian A-60 apparatus, TMS internal standard. We are indebted to Mr. George Robertson and Mr. Rudolf Oeckinghaus for microanalyses, to Miss Ruth Behnke, Miss Natalie Cahoon, Mr. Mike Hotolski, Mr. Charles Navarro, and Mr. Anis Hamden of the staff of Mr. Louis Dorfman for spectral data, and to Mrs. Angela Aretakis for literature search work.

dehydic acid (1) which dissolved readily (mild exothermic effect). After *ca.* 5 min, additional ethyl cyanoacetate (12 g) was added. A stream of anhydrous $NH_3$ was passed into the solution without cooling, resulting in an exothermic effect and separation of white crystals. After the suspension had been allowed to stand overnight, the solid salt was collected, washed with methanol, and dissolved in water and the solution was acidified with dilute HCl. On standing there appeared a mass of crystals which were collected (two crops), washed with water sparingly, and dried: yield 22.9 g (76%); mp 185–187° dec (discolor from 175°), not raised on recrystallization from methanol; ir 3.12 (int, broad), 4.41 (weak), and 5.73–5.85 $\mu$; uv 220–227 nm ($\epsilon$ 8760) and 274 (1510).

*Anal.* Calcd for $C_{14}H_9N_3O_4$: C, 59.36; H, 3.20; N, 14.84. Found: C, 59.02; H, 2.99; N, 14.68.

**o-(1,2-Dicyanoethyl)benzoic Acid (6).**—Reaction of 3.0 g of Na in 180 ml of methanol, 14 ml of ethyl cyanoacetate, and 18.4 g of 1 was carried out as described for 2, after which a solution of 6.8 g of NaCN in 40 ml of water was added, resulting in dissolution of the sodium salt which had separated. The solution was boiled for 3.5 hr on a steam cone, allowing most of the methanol to escape. The cooled, diluted (water) solution on acidification effervesced and an oil separated; an ether extract of the oil was washed with water, dried ($MgSO_4$), and evaporated. The residue crystallized slowly in the presence of ether, giving on trituration with this solvent 7 g of crystals: mp *ca.* 165–166° dec (sinter from 120°) after recrystallization from ether; ir 4.43 and 5.90 $\mu$; uv 227 nm ($\epsilon$ 8730) and 274 (1270) with inflection at 282 (1060). The compound was unstable, the crystalline material becoming sticky on standing.

*Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.25; H, 4.18; N, 13.86.

The tricarboxylic acid corresponding to 6 was obtained by heating a sample of 6 with 20 parts of concentrated HCl on a steam code for 3 hr (excess reagent was evaporated); an ethyl acetate extract was dried ($MgSO_4$) and evaporated and the residue was triturated with ether and recrystallized from ethyl acetate: colorless crystals; mp 190–192° dec; ir 5.81–5.92 $\mu$ and broad OH and zwitterion bands; uv 226 nm ($\epsilon$ 7360) and 276 (1140).

*Anal.* Calcd for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.21; H, 4.12.

Homophthalimide 9 was obtained when a sample of 6 was refluxed for 3.5 hr with 50–100 parts of saturated methanolic HCl, the excess reagent was evaporated, the residue was treated with water, and the resulting crude crystals were recrystallized from ether: mp 185.5–187°; ir 5.80, 5.92, and 6.24 $\mu$, and bonded NH band; uv 239 nm ($\epsilon$ 10,890), 280–285 (1407), 290 (1470), and 300–308 (980).

*Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.92; H, 4.58; N, 6.23.

**α-Carbomethoxy-α-3-phthalidylacetamide (4).**—Cyano ester 2 (21 g) on mixing with PPA (88 g) gave a solution slowly, with moderate exothermic effect (temperature rise to 60°). The solution was heated at 100° with stirring for 1 hr. Hydrolysis of the cooled PPA solution with 700 ml of ice water gave colorless crystals which were collected, washed with water, and dried, yield 17 g. Trituration with methanol and recrystallization from ethyl acetate afforded crystals: mp 198–200°; ir 2.98, 3.14, 5.71–5.76 (doublet), and 5.97 $\mu$; uv 228 nm ($\epsilon$ 9020), 273 (2570), and 280 (2570). The compound dissolved rather readily in dilute NaOH solution but not in $NaHCO_3$ solution. The amide ester lactone resisted further treatment with PPA.

*Anal.* Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.29; N, 5.49.

**o-(2-Carbomethoxy-2-cyanoethyl)benzoic Acid (5).**—Hydrogenation of 23.4 g of 2 in 250 ml of ethyl acetate in the presence of 6 g of 10% Pd/C at 45-lb gauge pressure (Parr apparatus; 4-l. reserve tank) resulted in a pressure drop of 8 lb in 17 min. At this point the solution was filtered and evaporated; the residue crystallized readily in the presence of ether, giving 17 g of triturated product. Recrystallization from ether gave colorless crystals: mp 126.5–128°; soluble in $NaHCO_3$ solution; ir 4.46, 5.77, and 5.95 $\mu$; uv 228 nm ($\epsilon$ 8500) and 277 (1560) with inflection at 285 (1310).

*Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.04; H, 4.92; N, 6.03.

**o-(2-Carbamoyl-2-carbomethoxy)benzoic Acid (7).**—Hydrogenation (45-lb gauge) of 10.1 g of 4 in 200 ml of ethyl acetate and 150 ml of ethanol in the presence of 3 g of 10% Pd/C at 65° for 3 hr, filtration, and evaporation of the solution gave 6.5 g of colorless crystals: mp 206–208°, raised on recrystallization (EtOAc) to mp 209–210°; soluble in $NaHCO_3$ solution (slowly); ir 5.75, 5.96, 6.07 and $NH_2$ bands (2.99, 3.18 $\mu$); uv 228 nm ($\epsilon$ 7960) and 278 (1200).

*Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.35; H, 5.24; N, 5.49.

**2-Carbomethoxy-1-indanone-2-carboxamide (8).**—A mixture of 6 g of acid nitrile ester 5 and 70 g of PPA was stirred and heated (steam cone) for 1 hr. After ice water hydrolysis of the cooled, bright red-orange (greenish fluorescent) PPA solution, the crude material was extracted with ethyl acetate–ether. The washed ($NaHCO_3$ solution, water) and dried ($MgSO_4$) organic solution gave bright orange, semisolid material. A methanol solution of the crude material was filtered to remove *ca.* 0.8 g of a crystalline, bright yellow by-product (mp 271–273° dec after recrystallization from methanol; ir 5.90–5.95, 6.12–6.18 $\mu$; uv $\lambda_{max}$ 266, 305, and 410 nm; $M^+$ 301 in mass spectrum) whose exact constitution was not established.

On evaporation of the MeOH solution, the main product 8 crystallized, and with the aid of ether there was isolated *ca.* 4 g as discolored crystals, mp 153–156°. Recrystallization from ethyl acetate gave colorless crystals: mp 158–160°; ir 2.95, 3.13, 5.72–5.82 (doublet), and 5.96 $\mu$; uv 251 nm ($\epsilon$ 13,650) and 296 (2670); positive test (red precipitate) with 2,4-dinitrophenylhydrazine.

*Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.90; H, 4.82; N, 6.01.

**2-Benzazepine-1,3-dione-4-carboxamide (11). A. Condensation.**—Condensation of sodiomalononitrile (prepared by adding 18.2 g of malononitrile to a solution of 6.3 g of Na in 250 ml of methanol) with 1 (40.5 g), as in the preparation of 2, resulted in rapid dissolution of the phthalaldehydic acid as it was added. The bright yellow, methanol solution was warmed gently for 10 min on a steam cone, allowed to stand for 1 hr, and, since there was no separation of a sodium salt, the solution was evaporated while warming gently (15 min) to remove most of the methanol. On addition of water, a clear, yellow solution was obtained. This was chilled and acidified with dilute HCl. The resulting yellow oil was extracted with ether, and the washed (water) and dried ($MgSO_4$) ether solution was evaporated, giving *ca.* 30 g of yellow, viscous oil, hardening to a cake of sticky, yellow solid after several days, mp *ca.* 110–115°; trituration with ether–ethyl acetate gave material, mp *ca.* 143–149°, but no solvent suitable for recrystallization of the rather unstable material could be found. It was for the most part soluble in $NaHCO_3$, and ir (2.78–2.91, 3.10, 4.46, 5.80, and 5.97 $\mu$) indicated structure 10, admixed with corresponding lactone and possibly also corresponding amides; uv $\lambda_{max}$ 214, 292 nm and high end absorption.

**B. Cyclization.**—Crude A product (18.5 g) and PPA (160 g) were stirred and heated for 5 min on a steam cone, which soon produced a bright red-orange solution (longer heating resulted in evident decomposition, with frothing, leading to a dark brown color). The PPA solution was allowed to stand for 1.5 hr while cooling gradually to room temperature, and then it was hydrolyzed with *ca.* 1 l. of ice and water. The resulting yellow solid was collected, washed with water, and triturated with $NaHCO_3$ solution, refiltered, washed again with water, and triturated with methanol (or acetone) to remove greenish-orange, oily impurities. There remained 3.6 g of yellow crystals, mp 240–250° dec (softening at 230°). Further trituration with methanol raised the melting point to 247–251°, and finally recrystallization from ethyl acetate gave a pure sample as nearly colorless crystals: mp 268–270° dec; ir 2.96, 3.15, 5.85–5.96, 6.07 $\mu$; uv 225 nm ($\epsilon$ 29,000) and 310 (10,130); nmr (DMSO) $\delta$ 11.6 (s, 1, exchanges with $D_2O$, imide NH), 8.5–7.6 (m, 6, exchanges with 2 $D_2O$, ArH and $CONH_2$), 8.1 (s, 1, vinyl H).

*Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.46; H, 3.84; N, 12.68.

The compound had a remarkably powerful sternutatory effect on its investigator.

**4,5-Dihydro-2-benzazepine-1,3-dione-4-carboxamide (12).**—A solution of 1.2 g of 11 in 300 ml of EtOAc containing 1.5 g of 10% Pd/C was shaken under $H_2$ (45 lb) at 70–75° for 2.5 hr. Filtration of the catalyst and evaporation of the solvent gave a quantitative yield of colorless crystals, mp 217–222°. Recrystallization from EtOAc afforded a pure sample: mp 219–221°; ir 2.91, 3.15, 3.25, 5.92–5.99, and 6.17–6.25 $\mu$; uv 241 nm ($\epsilon$ 10,950) and 282 (1660); nmr (DMSO) $\delta$ 10.7 (s, 1, exchanges with $D_2O$, imide NH), 8.1–6.9 (m, 6, exchanges with 2 $D_2O$, ArH and

$CONH_2$), 3.72 (t, 1, $J$ = 5 Hz, proton 4), and 3.3 (d, 2, $J$ = 5 Hz, methylene).

*Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84; mol wt, 218.21. Found: C, 60.71; H, 4.39; N, 12.54; $M^+$, 218.

The compound did *not* induce sneezing.

**2-Benzazepine-1,3-dione (14). A. *cis-o*-Carboxycinnamonitrile (13)** was prepared, following literature procedure, by treating 21 g of 2-nitroso-1-naphthol in 1 l. of ligroin with 26 g of $PCl_5$, stirring for several hours while HCl was evolved copiously, allowing the mixture to stand for 3 days, and taking the crude solid into *ca.* 200 ml of 10% NaOH solution; acidification of the filtered solution with 15% HCl and recrystallization of the cyano acid from methanol gave crystals of **13**, mp 177–179° (lit.[9] mp 172°, 179°).

**B. PPA Closure.**—A suspension of 2 g of **13** in 42 g of PPA was heated in a steam cone and stirred for 0.5 hr. The purple-brown solution was cooled and hydrolyzed with cold water; the crude crystals were collected, washed with water, triturated with dilute $NaHCO_3$ solution, and again collected, washed with water, and dried. Recrystallization from ether, filtering the solution free of dark sediment, gave 0.5 g of crystals: mp 142–143°; ir 3.14–3.28 (bonded NH), and 6.03–6.06 $\mu$, with shoulders at 5.90–5.95 $\mu$; uv 224 nm ($\epsilon$ 31,080), 281 (8600), and 321 (3830), with inflections at 288 (8360) and 306 (5740); nmr ($CDCl_3$) $\delta$ 9.4 (m, 1, exchanges with $D_2O$, imide NH), 8.5 (m, 1, proton 9), 7.6 (m, 3, ArH), 7.16 (d, 1, $J$ = 12.5 Hz, proton 5), and 6.4 [q, 1, $J$ = 12.5 Hz, coupling to proton 5, $J'$ = 2.5 Hz (long range coupling to imide NH, disappearing on $D_2O$ exchange of NH), proton 4].

*Anal.* Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.49; H, 4.14; N, 8.03.

**4,5-Dihydro-2-benzazepine-1,3-dione (15).**—Hydrogenation of **14** as for **11** at 65° for 1.5–2 hr, and evaporation of the filtered, colorless solution, gave crystals, from ethyl acetate–ether: mp 118.5–120.5°; ir 3.11–3.25, 5.90, and 6.00 $\mu$; uv 239 nm ($\epsilon$ 12,870) and 282 (1760); nmr ($CDCl_3$) $\delta$ 8.76 (m, 1, exchanges with $D_2O$, imide NH), 8.1 (m, 1, proton 9), 7.34 (m, 3, ArH), and 2.96 (resembling q, 4, $J$'s not first order, methylenes).

*Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.22; H, 5.25; N, 7.93.

**Registry No.**—**2**, 36004-42-9; **3**, 36004-43-0; **4**, 36004-44-1; **5**, 36004-45-2; **6**, 36015-22-2; **6** (tricarboxylic acid derivative), 36004-46-3; **7**, 36004-47-4; **8**, 36004-48-5; **9**, 36004-49-6; **11**, 36004-50-9; **12**, 36004-51-0; **14**, 36004-52-1; **15**, 36004-53-2.

## Synthesis of Some 7-Aryl-6-azapteridines from 1,2,4-Triazine Intermediates

EDWARD C. TAYLOR* AND STEPHEN F. MARTIN[1]

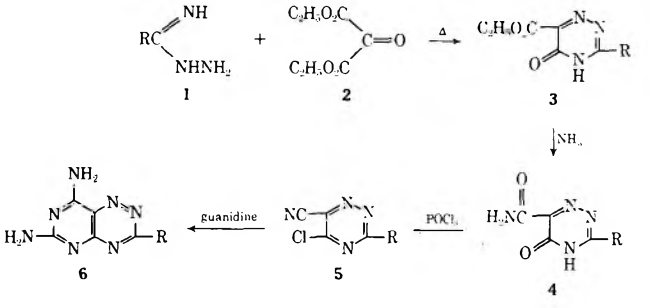
*Department of Chemistry, Princeton University, Princeton, New Jersey 08540*

*Received May 26, 1972*

Interest in the pyrimido[4,5-*e*]-*as*-triazine (6-azapteridine) and pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) ring systems has intensified recently[2-7] as a consequence of the discovery that certain derivatives of the former ring system exhibit antiviral activity,[8] and that a number of broad-spectrum antibiotics (toxoflavin, fervenulin, and 2-methylfervenulone) are derivatives of the 7-azapteridine ring system.[9] We have explored the possibility of utilizing a common intermediate for the synthesis of both isomeric ring systems, and our results are summarized in this brief report.

The condensation of amidrazones with $\alpha,\beta$-dicarbonyl compounds to give *as*-triazines is well known,[10-12] but none of the many *as*-triazines thus far prepared by this route possesses substituent groups suitable for subsequent cyclization to an azapteridine. It occurred to us that the reaction of amidrazones (**1**) with diethyl oxomalonate (**2**) should afford *as*-triazines[13] (**3**) which could readily be converted into 6-azapteridines (**6**) by the sequence of reactions depicted in Scheme I.

SCHEME I




Indeed, this concept proved to be successful when R = aryl, but it failed at the dehydration–chlorination step (**4** → **5**) with R = alkyl ($CH_3$, $C_2H_5$). Many different reaction conditions were explored ($POCl_3$, $POCl_3$–pyridine, $POCl_3$–DMF, $SOCl_2$–pyridine, $SOCl_2$–DMF), but in all cases only resinous, uncharacterizable products were obtained.

There is little ambiguity as to the structure of the condensation products formed in the above reaction (see Scheme I), since the keto grouping of diethyl oxomalonate is considerably more reactive than the ester groups, and $N^1$ of the amidrazone[14] is the most nucleophilic nitrogen. However, the structural assignments were confirmed independently by the unequivocal synthesis of **3** (R = $C_6H_5$, $CH_3$) by the reaction of the hydrazone of diethyl oxomalonate (**8**)[15] with the imidate esters **7** (R = $C_6H_5$, $CH_3$) (see Scheme II). The products of this latter condensation were identical in every respect with the corresponding compounds prepared by the alternate procedure described in Scheme I.

In principle, protection of $N^1$ of the amidrazone fol-

(1) NIH Predoctoral Fellow, 1969–1972.

(2) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **36**, 3502 (1971), and references cited therein.

(3) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Heterocycl. Chem.*, **8**, 1099 (1971).

(4) F. Yoneda, K. Shinomura, and S. Nishigaki, *Tetrahedron Lett.*, 851 (1971).

(5) F. Yoneda, M. Kanahori, and S. Nishigaki, *J. Heterocycl. Chem.*, **8**, 523 (1971).

(6) F. Yoneda, M. Kanahori, K. Ogiwara, and S. Nishigaki, *ibid.*, **7**, 1443 (1970).

(7) D. J. Brown and T. Sugimoto, *J. Chem. Soc. C*, 2616 (1971).

(8) C. Kuchler, W. Kuchler, and L. Heinisch, *Arzneim.-Forsch.*, **16**, 1122 (1966).

(9) E. C. Taylor and S. F. Martin, *J. Org. Chem.*, **35**, 3792 (1970), and references cited therein.

(10) R. L. Jones and J. R. Kershaw, *Rev. Pure Appl. Chem.*, **21**, 23 (1971).

(11) H. Neunhoeffer, H. Hennig, H.-W. Fruhauf, and M. Mutterer, *Tetrahedron Lett.*, 3147 (1969).

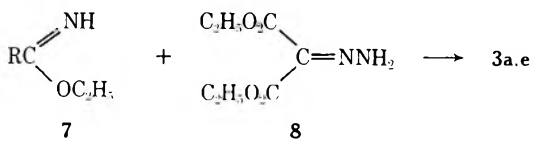
(12) M. Brugger, H. Wamhoff, and F. Korte, *Justus Liebigs Ann. Chem.*, **755**, 101 (1972).

(13) This route to *as*-triazines is not new; diethyl oxomalonate and thiosemicarbazide, for example, are known to give **3**, R = SH [R. B. Barlow and A. D. Welch, *J. Amer. Chem. Soc.*, **78**, 1258 (1956)].

(14) See H. Rapoport and R. M. Bonner, *J. Amer. Chem. Soc.*, **72**, 2783 (1950), for the nomenclature of amidrazones.

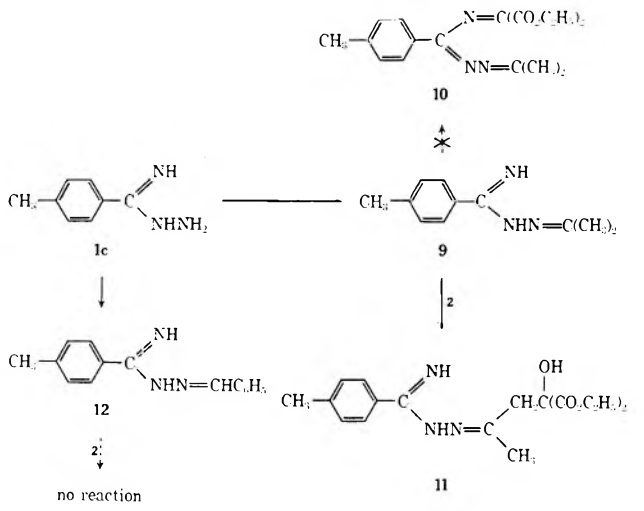
(15) E. Ciganek, *J. Org. Chem.*, **30**, 4366 (1965).

SCHEME II



lowed by condensation with diethyl oxomalonate should result in initial imine formation; removal of the protecting group and subsequent intramolecular cyclization would then lead to the isomeric 7-azapteridine ring system, thus realizing our objective of preparing both ring systems from a common precursor. Unfortunately, our efforts thus far to effect this reverse condensation mode have been unsuccessful. Compound **1c** was successfully converted into its isopropylidene derivative **9** by reaction with acetone, but subsequent reaction with diethyl oxomalonate (**2**) proceeded anomalously to give **11** rather than **10**, the expected product. In an effort to avoid this unexpected reaction, **1c** was converted into its benzylidene derivative **12**, but this failed to react with diethyl oxomalonate (see Scheme III).

SCHEME III



## Experimental Section

**General.**—Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Imidate ester hydrochlorides were prepared from the corresponding nitriles using standard procedures.[16] All of the aryl-substituted amidrazones were prepared by the reaction of anhydrous hydrazine (1 equiv) with the appropriate imino ester free base (as described below for *p*-chlorobenzamidrazone) except for the case of **1d** (R = 2-pyridyl) which was prepared by the method of Case.[17] Aliphatic amidrazones were prepared by the method of Wright, Halliday, and Davis.[18]

***p*-Chlorobenzamidrazone (1b).**—Ethyl *p*-chlorobenzimidate hydrochloride (10.0 g, 0.0454 mol) was shaken with 100 ml of 5% aqueous sodium hydroxide solution and 150 ml of ether. The aqueous layer was extracted with ether (1 × 75 ml); the combined ether layers were washed with water until they were no longer basic and then dried over 5A molecular sieves. The ether was evaporated under reduced pressure giving 7.2 g (0.039 mol) of crude ethyl *p*-chlorobenzimidate. A solution of 97% anhydrous hydrazine (1.30 g, 0.039 mol) in a mixture of 100 ml of anhydrous ether and 15 ml of anhydrous ethanol was added and the solution allowed to stand at 0° for 2 days. The excess solvent was evaporated under reduced pressure and the product recrystallized from isopropyl ether to give 4.28 g (56%) of white flakes, mp 87–89°. *Anal.* Calcd for $C_7H_8N_3Cl$: C, 49.57; H, 4.75; N, 24.79; Cl, 20.90. Found: C, 49.24; H, 4.72; N, 24.96; Cl, 21.21.

**6-Carbethoxy-3-phenyl-5(4*H*)-*as*-triazinone (3a). Method A.**[19]—To a solution of diethyl oxomalonate (**2**) (3.64 g, 20.9 mmol) dissolved in 10 ml of isopropyl alcohol was slowly added a solution of benzamidrazone (3.25 g, 20.9 mmol) in 20 ml of isopropyl alcohol. The solution was stirred at room temperature for 6 hr and then refluxed 2 hr to complete the cyclization. Evaporation of the excess solvent under reduced pressure, trituration of the residue with a small volume of cold ethyl acetate (*ca.* 20 ml), and recrystallization from ethyl acetate afforded 3.28 g (64%) of a colorless granular solid, mp 202–203°. *Anal.* Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.62; H, 4.59; N, 17.09.

**Method B.**—A solution of the hydrazone of diethyl oxomalonate (1.26 g, 6.72 mmol) and ethyl benzimidate (1.00 g, 6.72 mmol) in 25 ml of isopropyl alcohol was refluxed 16 hr. The excess solvent was evaporated under reduced pressure and about 10 ml of ethyl acetate added to the residue. Cooling and filtering gave 0.61 g of crude product which was recrystallized from a small volume of ethyl acetate, yielding 0.43 g (26%). No attempt was made to optimize the yield. The product was identical with that obtained by method A.

The following compounds were prepared analogously by method A.

**6-Carbethoxy-3-(*p*-chlorophenyl)-5(4*H*)-*as*-triazinone (3b):** 62%, mp 244° dec (translucent plates from isopropyl alcohol). *Anal.* Calcd for $C_{12}H_{10}N_3ClO_3$: C, 51.53; H, 3.36; N, 15.03; Cl, 12.68. Found: C, 51.40; H, 3.57; N, 14.91; Cl, 12.86.

**6-Carbethoxy-3-(*p*-tolyl)-5(4*H*)-*as*-triazinone (3c):** 53%, mp 222–223° dec (colorless needles from isopropyl alcohol). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.01; H, 5.04; N, 16.16.

**6-Carbethoxy-3-(2-pyridyl)-5(4*H*)-*as*-triazinone (3d):** 62%, mp 142–143° (very fine colorless needles from ethyl acetate). *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.55; H, 4.21; N, 22.80.

**6-Carbethoxy-3-methyl-5(4*H*)-*as*-triazinone (3e)** (method A): 55%, mp 160–161° (colorless granular solid from ethyl acetate). *Anal.* Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.82; H, 5.14; N, 23.13.

Method B gave 68% yield.

**6-Carbethoxy-3-ethyl-5(4*H*)-*as*-triazinone (3f):** 61%, mp 202–204° (colorless granular solid from benzene–ether). *Anal.* Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.46; H, 5.89; N, 21.48.

**6-Carbamoyl-3-phenyl-5(4*H*)-*as*-triazinone (4a).**—Compound **3a** (1.75 g) was suspended in 50 ml of anhydrous methanol and the mixture saturated at 0° with dry ammonia gas. The resulting mixture was stirred for 18 hr at room temperature and concentrated to about half of its original volume under reduced pressure; the product was collected by filtration and then recrystallized from isopropyl alcohol to give 1.45 g (83%) of fine colorless needles, mp 301° dec. *Anal.* Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.58; H, 3.77; N, 25.88.

The following compounds were prepared analogously.

**6-Carbamoyl-3-(*p*-chlorophenyl)-5(4*H*)-*as*-triazinone (4b):** 85%, mp 322–323° dec (colorless flakes from ethanol). *Anal.* Calcd for $C_{10}H_7N_4ClO_2$: C, 47.92; H, 2.81; N, 22.35. Found: C, 48.05; H, 2.77; N, 22.40.

**6-Carbamoyl-3-(*p*-tolyl)-5(4*H*)-*as*-triazinone (4c):** 84%, mp 319–320° dec (white microcrystalline solid from isopropyl alcohol). *Anal.* Calcd for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.43; H, 4.52; N, 24.48.

**6-Carbamoyl-3-(2-pyridyl)-5(4*H*)-*as*-triazinone (4d):** 89%, mp 294–295° dec (colorless granular solid from ethanol). *Anal.*

(16) (a) S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, **64**, 1825 (1942); (b) "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1943, p 6.

(17) F. H. Case, *J. Org. Chem.*, **30**, 931 (1965).

(18) G. C. Wright, R. P. Halliday, and C. S. Davis, *J. Pharm. Sci.*, **59**, 105 (1970).

(19) NOTE ADDED IN PROOF.—The preparation of this compound (mp 197–198° from ethanol) by the same route, and its conversion into several 6-azapteridines by reaction with $PCl_5$ to give 6-carbethoxy-5-chloro-3-phenyl-*as*-triazine, followed by condensation with acetamidine, benzamidine, and 1,3-dimethylurea, has recently been described [M. Brugger, H. Wamhoff, and F. Korte, *Justus Liebigs Ann. Chem.*, **758**, 173 (1972)].

Calcd for $C_9H_7N_5O_2$: C, 49.77; H, 3.25; N, 32.25. Found: C, 49.94; H, 3.20; N, 32.38.

**6-Carbamoyl-3-methyl-5(4*H*)-*as*-triazinone** (**4e**): 68%, mp 270° dec (cream-colored powdery solid from isopropyl alcohol). *Anal.* Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.80; H, 3.92; N, 36.53.

**6-Carbamoyl-3-ethyl-5(4*H*)-*as*-triazinone** (**4f**): 57%, mp 266° dec (short pale yellow needles from isopropyl alcohol). *Anal.* Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.66; H, 4.80; N, 33.25.

**5-Chloro-6-cyano-3-phenyl-*as*-triazine** (**5a**).—To a cooled mixture of phosphorus oxychloride (5 ml) and anhydrous pyridine (0.92 g, 11.6 mmol) was added portionwise with stirring 4a (0.50 g, 2.32 mmol). The mixture was gently refluxed for 15 min, the excess phosphorus oxychloride evaporated under reduced pressure, and the viscous residue poured over ice. The aqueous solution was neutralized with sodium bicarbonate and then extracted with chloroform (4 × 25 ml). The combined extracts were dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Recrystallization of the crude product from benzene–hexane afforded 0.34 g (68%) of yellow plates, mp 184–185°. *Anal.* Calcd for $C_{10}H_5N_4Cl$: C, 55.44; H, 2.32; N, 25.86. Found: C, 55.49; H, 2.20; N, 25.82.

The following compounds were prepared analogously.

**5-Chloro-6-cyano-3-(*p*-chlorophenyl)-*as*-triazine** (**5b**): 69%, mp 152–153° dec (very fine pale yellow needles from benzene–hexane). *Anal.* Calcd for $C_{10}H_4N_4Cl_2$: C, 47.83; H, 1.61; N, 22.31. Found: C, 47.64; H, 1.63; N, 21.99.

**5-Chloro-6-cyano-3-(*p*-tolyl)-*as*-triazine** (**5c**): 70%, mp 201–202° (yellow plates from acetonitrile). *Anal.* Calcd for $C_{11}H_7N_4Cl$: C, 57.27; H, 3.05; N, 24.29. Found: C, 57.25; H, 3.01; N, 24.28.

**5-Chloro-6-cyano-3-(2-pyridyl)-*as*-triazine** (**5d**): 73%, mp 151–153° dec (blunt yellow prisms from benzene–hexane). *Anal.* Calcd for $C_9H_4N_5Cl$: C, 49.67; H, 1.85; N, 32.19. Found: C, 49.47; H, 1.64; N, 32.15.

**2,4-Diamino-7-phenylpyrimido[4,5-*e*]-*as*-triazine** (**6a**).—Compound **5a** (0.25 g, 1.15 mmol) was suspended in a methanolic solution of guanidine (prepared from guanidine hydrochloride (0.22 g, 2.30 mmol) and metallic sodium (0.053 g, 2.30 g-atoms) in 10 ml of anhydrous methanol) and the mixture refluxed for 16 hr. The mixture was cooled and filtered; the solid was washed with water and recrystallized from dimethylformamide to give 0.15 g (55%) of a yellow microcrystalline solid, mp >300°. *Anal.* Calcd for $C_{11}H_9N_7$: C, 55.22; H, 3.79; N, 40.99. Found: C, 55.22; H, 3.93; N, 41.24.

The following compounds were prepared analogously.

**2,4-Diamino-7-(*p*-chlorophenyl)pyrimido[4,5-*e*]-*as*-triazine** (**6b**): 56%, mp >300° (yellow microcrystalline solid from dimethylformamide). *Anal.* Calcd for $C_{11}H_8N_7Cl$: C, 48.27; H, 2.95; N, 35.83. Found: C, 48.16; H, 2.91; N, 35.77.

**2,4-Diamino-7-(*p*-tolyl)pyrimido[4,5-*e*]-*as*-triazine** (**6c**): 64%, mp >300° (yellow microcrystalline solid from dimethylformamide). *Anal.* Calcd for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.72. Found: C, 56.98; H, 4.52; N, 38.74.

**2,4-Diamino-7-(2-pyridyl)pyrimido[4,5-*e*]-*as*-triazine** (**6d**): 44%, mp >300° (yellow microcrystalline solid from dimethylformamide). *Anal.* Calcd for $C_{10}H_8N_8$: C, 49.99; H, 3.36; N, 46.65. Found: C, 49.88; H, 3.40; N, 46.75.

***N*¹-Isopropylidine-*p*-toluamidrazone** (**9**).—*p*-Toluamidrazone (6.00 g) was dissolved in 100 ml of acetone and the solution stirred at room temperature for 30 min. Evaporation of the excess solvent under reduced pressure and recrystallization from hexane afforded 6.41 g (84%) of colorless needles, mp 72–73°. *Anal.* Calcd for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.74; H, 8.06; M, 22.34.

**Reaction of *N*¹-Isopropylidene-*p*-toluamidrazone with Diethyl Oxomalonate. Formation of 11.**—To a solution of **9** (0.50 g, 2.65 mmol) in 10 ml of anhydrous benzene was added diethyl oxomalonate (**2**) (0.46 g, 2.65 mmol), and the solution was refluxed (Dean-Stark trap) for 3 hr. The excess solvent was evaporated under reduced pressure, the residual viscous oil dissolved in a minimum volume of hexane, and the solution cooled and filtered. Recrystallization from hexane gave 0.64 g (67%) of blunt colorless prisms, mp 78–79°. *Anal.* Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.33; H, 6.91; N, 11.37. Nmr ($CDCl_3$): $\delta$ 1.27 (t, 6), 2.15 (s, 3), 2.40 (s, 3), 3.18 (s, 2), 4.29 (q, 4), 7.23 (d, 2, $J$ = 8 Hz), 7.74 (d, 2, $J$ = 8 Hz).

**Registry No.**—**1b**, 36286-75-6; **3a**, 36286-76-7; **3b**, 36286-77-8; **3c**, 36286-78-9; **3d**, 36286-79-0; **3e**, 36286-80-3; **3f**, 36286-81-4; **4a**, 36294-41-4; **4b**, 36286-82-5; **4c**, 36286-83-6; **4d**, 36286-84-7; **4e**, 36286-85-8; **4f**, 36286-86-9; **5a**, 36286-87-0; **5b**, 36286-88-1; **5c**, 36286-89-2; **5d**, 36286-90-5; **6a**, 36286-91-6; **6b**, 36286-92-7; **6c**, 36286-93-8; **6d**, 36286-94-9; **9**, 36286-95-0; **11**, 36286-96-1.

## Chloral–Hydrazone Adducts

F. E. CONDON* AND J. P. TRIVEDI

*Department of Chemistry, The City College of the City University of New York, New York 10031*

*Received March 20, 1972*

The acid-catalyzed oxidative dimerization of formaldehyde dimethylhydrazone (**1**), to glyoxal bis-dimethylhydrazone (**3**) by way of the head-to-head dimer, 2,2-dimethylhydrazinoacetaldehyde dimethylhydrazone (**2**) (eq 1), was described recently.[1] We

$$\underset{\mathbf{1}}{2Me_2NN{=}CH_2} \xrightarrow{H^+} \underset{\mathbf{2}}{[Me_2NN{=}CHCH_2NHNMe_2]} \xrightarrow{-2H} Me_2NN{=}CHCH{=}NNMe_2 \quad \underset{\mathbf{3}}{} \quad (1)$$

now wish to report the spontaneous addition of hydrazones, including **1**, to chloral (trichloroacetaldehyde, **4**), as in eq 2, a process that is analogous to the first step in eq 1.

$$R_1R_2NN{=}CHR_3 + \underset{\mathbf{4}}{Cl_3CCHO} \longrightarrow \underset{\mathbf{5}}{R_1R_2NN{=}CR_3CHOHCCl_3} \quad (2)$$

Chloral–hydrazone adducts that have been prepared and characterized are described in Table I. Those obtained from formaldehyde hydrazones are formulated as hydrazones of 2-hydroxy-3,3,3-trichloro-1-propanone (**5**, $R_3$ = H) on the bases of elemental analyses and the nmr spectral data, which include tests for exchangeable hydrogen with $D_2O$ in acetone-$d_6$. Adducts were obtained also from benzaldehyde dimethylhydrazone and from formaldehyde methylphenylhydrazone, but they were too unstable to permit complete characterization.

Most of the adducts were light yellow, crystalline solids; one, from formaldehyde diethylhydrazone, was an oil. They all decomposed to black tars if kept at room temperature, but most could be kept indefinitely under refrigeration at −10°. Half-lives at room temperature ranged from about 1 hr to about 4 days. The decomposition products gave a positive test for chloride ion with aqueous silver nitrate.

The first chloral–hydrazone adduct resulted from an attempt to prepare chloral dimethylhydrazone by an exchange reaction between chloral and **1** under anhydrous conditions, since the reaction of chloral with 1,1-dimethylhydrazine gave only tarry decomposition products.[2] The formation of an adduct with structure **5** was unexpected, but the result can be rationalized in terms of structural features peculiar to

(1) F. E. Condon and D. Farcasiu, *J. Amer. Chem. Soc.*, **92**, 6625 (1970).
(2) *Cf.* R. L. Hinman and D. Fulton, *ibid.*, **80**, 1895 (1958).

TABLE I
CHLORAL–HYDRAZONE ADDUCTS

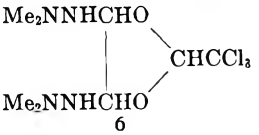
| Hydrazone | Method of prepn | Mp, °C | Approximate half-life at 30°, hr | Formula[a] | Nmr spectrum, δ, ppm (in $CD_3COCD_3$ with TMS) |
|---|---|---|---|---|---|
| $Me_2NN{=}CH_2$ | A, B (Adduct: 2-Hydroxy-3,3,3-trichloro-1-propanone dimethylhydrazone) | 65 | $10^2$ | $C_5H_9Cl_3N_2O$ | 6.60 (d, 1, $J$ = 5 Hz, =CH), 5.42 (broad s, 1, exchangeable, OH), 4.63 (d, 1, $J$ = 5 Hz, =CHCHOH), 2.85 [s, 6, $(CH_3)_2N$] |
| $EtMeNN{=}CH_2$[b] | B (Adduct: 2-Hydroxy-3,3,3-trichloro-1-propanone ethylmethylhydrazone) | 32[c] | $10^2$ | $C_6H_{11}Cl_3N_2O$ | 6.60 (d, 1, $J$ = 5 Hz, =CH), 5.53 (d, 1, $J$ = 7 Hz, exchangeable, OH), 4.66 (m, 1, =CHCHOH), 3.32 (q, 2, $J$ = 7 Hz, $CH_3CH_2N$), 2.78 (s, 3, $CH_3N$), 1.02 (t, 3, $J$ = 7 Hz, $CH_3CH_2N$) |
| $Et_2NN{=}CH_2$[b] | B (Adduct: 2-Hydroxy-3,3,3-trichloro-1-propanone diethylhydrazone) | Oil | $10^2$ | $C_7H_{13}Cl_3N_2O$[d] | 6.65 (d, 1, $J$ = 5 Hz, =CH), 4.65 (d, 1, $J$ = 5 Hz, =CHCHOH), 3.32 [q, 4, $J$ = 7 Hz, $(CH_3CH_2)_2N$], 3.2 (s, 1, exchangeable, OH), 1.12 [t, 6, $J$ = 7 Hz, $(CH_3CH_2)_2N$] |
| $[Me_2NN{=}CH{-}]_2$ | A | 78 | $10^3$ | $C_8H_{17}Cl_3N_4O_2$[e] | 7.03 (s, 2, NHCHO–), 6.6 (s, broad, 2, exchangeable, NH), 5.23 [s, 1, $(-O)_2CHCCl_3$], 2.82 [s, 12, $(CH_3)_2N$] |

[a] *Anal.* All C values ±0.38, H ±0.14 of theoretical, except where stated. [b] F. E. Condon, unpublished work. [c] $d^{25}D$ 1.3081 g/cm³ (supercooled liquid). [d] *Anal.* Calcd for $C_7H_{13}Cl_3N_2O$: C, 33.98; H, 5.30. Found: C, 35.67; H, 5.36. [e] 1:1 Adduct with chloral hydrate (**6**). *Anal.* Calcd for $C_8H_{17}Cl_3N_4O_2$: Cl, 18.24; N, 34.54. Found: Cl, 17.71; N, 34.27.

hydrazones on the one hand and to chloral on the other. In the hydrazone, the methylenic carbon is rendered nucleophilic by electron release from the more remote nitrogen,[3] $Me_2N^+{=}NCH_2^-$; and in chloral, electron withdrawal by three chlorine atoms imparts unusual stability to products of addition of nucleophilic reagents to the carbonyl group, including water ("chloral hydrate") and hydrazine.[4]

Other, simple aldehydes apparently do not react with hydrazones as does chloral. Formaldehyde dimethylhydrazone (**1**) is commonly obtained in high yield by reaction of dimethylhydrazine with an *excess* of formaldehyde.[5] The reaction is not complicated by further reaction of **1** with the excess formaldehyde.

Reaction of chloral with glyoxal bisdimethylhydrazone (**3**) was carried out with the expectation of obtaining a bischloral adduct. The product, however, corresponded to a 1:1 adduct of **3** with chloral *hydrate* and its nmr spectrum (Table I) is consistent with its formation as 2-trichloromethyl-4,5-bis(2,2-dimethylhydrazino)dioxolane (**6**). The product **6** was much



**6**

more stable than the adducts **5**; **6** had a half-life at room temperature of several weeks.

Structure **6** can exist as three geometric isomers (two meso forms and a racemate). The simplicity of the nmr spectrum (the hydrogens on C-4 and C-5 giving a singlet) indicates a high degree of symmetry, characteristic of a meso form, with the hydrogens on C-4 and C-5 cis to one another; it does not permit a decision regarding the relative configuration of the hydrogen on C-2.

(3) S. F. Nelson, *J. Org. Chem.*, **34**, 2248 (1969).
(4) C. N. Yiannios, A. C. Hazy, and J. V. Karabinos, *ibid.*, **33**, 2076 (1968).
(5) J. B. Class, J. G. Aston, and T. B. Oakwood, *J. Amer. Chem. Soc.*, **75**, 2937 (1953).

### *Experimental Section*

**Method A.**—Chloral (containing about 4% of a stabilizer) was added in the course of about 1 hr to an equivalent amount of the hydrazone with stirring and cooling to maintain the temperature at 10–15°. Crystal formation began almost immediately and continued for several hours under refrigeration. The crude solid product thus obtained in quantitative yield was purified with some loss by recrystallization from petroleum ether (bp 30–60°) or a mixture of ethyl ether and petroleum ether.

**Method B.**—A 10% aqueous solution of chloral was prepared and freed of stabilizer by filtration. An equivalent amount of the hydrazone (or of formaldehyde and 1,1-dimethylhydrazine) was dissolved in the solution, and the mixture was allowed to stand at room temperature for several hours or under refrigeration for a day or two. The crystalline product or oil was separated. If crystalline, it was purified as before. Oily products were washed several times with cold water and then dried under vacuum without heating. An oily product from formaldehyde methylethylhydrazone crystallized after several days at −10°.

**Registry No.**—**5** ($R_1$ = $R_2$ = Me; $R_3$ = H), 36259-17-3; **5** ($R_1$ = Et; $R_2$ = Me, $R_3$ = H), 36259-19-5; **5** ($R_1$ = $R_2$ = Et; $R_3$ = H), 36259-18-4; **6**, 36259-20-8.

## Synthesis of Adamantane Derivatives. XXI.[1] A Facile Fragmentation of 4-Azatricyclo[5.3.1.1$^{3,9}$]dodecan-5-one to 7-Cyanomethylbicyclo[3.3.1]non-2-ene

TADASHI SASAKI,* SHOJI EGUCHI, AND MASATO MIZUTANI

*Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan*

*Received May 26, 1972*

We have previously reported that the Schmidt and Beckmann rearrangements of the homoadamantan-

(1) Part XX: T. Sasaki, S. Eguchi, T. Toru, and K. Itoh, *J. Amer. Chem. Soc.*, **94**, 1357 (1972).

4-one system afford normal rearrangement products together with some tetrazole derivatives, contrary to those of the adamantan-2-one system, where the Schmidt and Beckmann fissions have occurred extensively.[2-6] As an extension of these studies, this note describes a facile fragmentation of 4-azatricyclo[5.3.1.1$^{3,9}$]dodecan-5-one to 7-cyanomethylbicyclo[3.3.1]non-2-ene.

When *anti*-homoadamantan-4-one oxime (**1**) was treated with a large excess of polyphosphate ester (PPE) in chloroform under refluxing for 0.5 hr, two products, **2** and **3**, were obtained in 21 and 64% yields, respectively. The same reaction for 1 hr afforded only **3** in 79% yield. Compound **2** was characterized as the normal Beckmann rearrangement product, 4-azatricyclo[5.3.1.1$^{3,9}$]dodecan-5-one, by spectral comparison with an authentic sample[2] and by its reduction to 4-azatricyclo[5.3.1.1$^{3,9}$]dodecane (**4**) (Scheme I). Compound **3** was obtained as a colorless oil and had a molecular formula $C_{11}H_{15}N$ on the basis of analysis and mass spectral data, *m/e* 161 ($M^+$). Ir (neat) absorptions at 2280 and 1641 cm$^{-1}$ demonstrated the presence of C≡N and C=C moieties in **3**. The nmr ($CCl_4$) spectrum of **3** exhibited signals at $\tau$ 3.7–4.5 (m 2, CH=CH) and 7.3–8.6 (m, 13, other protons), which were shifted to $\tau$ 3.1–4.1 (m, 2), 5.48 (d, $J$ = 6.2 Hz, 2, $CHCH_2CN$), and 6.0–9.0 (m, 11) by an addition of the shift reagent, tris(dipivalomethanato)europium [Eu(dpm)$_3$/**3** = 0.459].[7] Thus, the structure of **3** was assigned as 7-cyanomethylbicyclo[3.3.1]non-2-ene. An endo configuration of the 7-cyanomethyl group was assignable from the mode of formation. The conclusive evidence of the assignment was obtained by conversion of **3** to ethyl bicyclo[3.3.1]nonan-3-*endo*-acetate (**7**) *via* **5** and **6**, and by an alternative synthesis of **7** from bicyclo[3.3.1]non-6-ene-3-*endo*-carboxylic acid (**8**)[6] *via* **9**, **10**, and **11** (Scheme I).

Treatment of **1** with phosphorus pentachloride also gave **3**; reactions with an equimolar amount of *p*-toluenesulfonyl chloride and with excess hydrogen chloride gave only **2** (Table I).

The data in Table I indicate that the longer reaction time favors the formation of the fission product **3** in the reactions of **1** with PPE and $PCl_5$. This fact suggests that **3** may be produced by a secondary reaction of **2** or its equivalent **12**. In fact, treatment of **2** with PPE and/or $PCl_5$ afforded the fission product **3** (Scheme I).

The facile ring fission of **2** can be ascribed to the large ring strain involved in the ring system.[8] The less strained 4-azatricyclo[4.3.1.1$^{3,8}$]undecan-5-one (**13**)[3-6] and monocyclic pyrrolidone **15** afforded no trace of the corresponding unsaturated nitrile derivatives **14** and **16** on treatment with PPE. Hence, the formation of **3** from **1** is explained by a secondary fission of the primarily produced **12** by the normal Beckmann rearrangement of **1**.[9]

**13** ⇢ **14** **15** ⇢ **16**

Scheme I

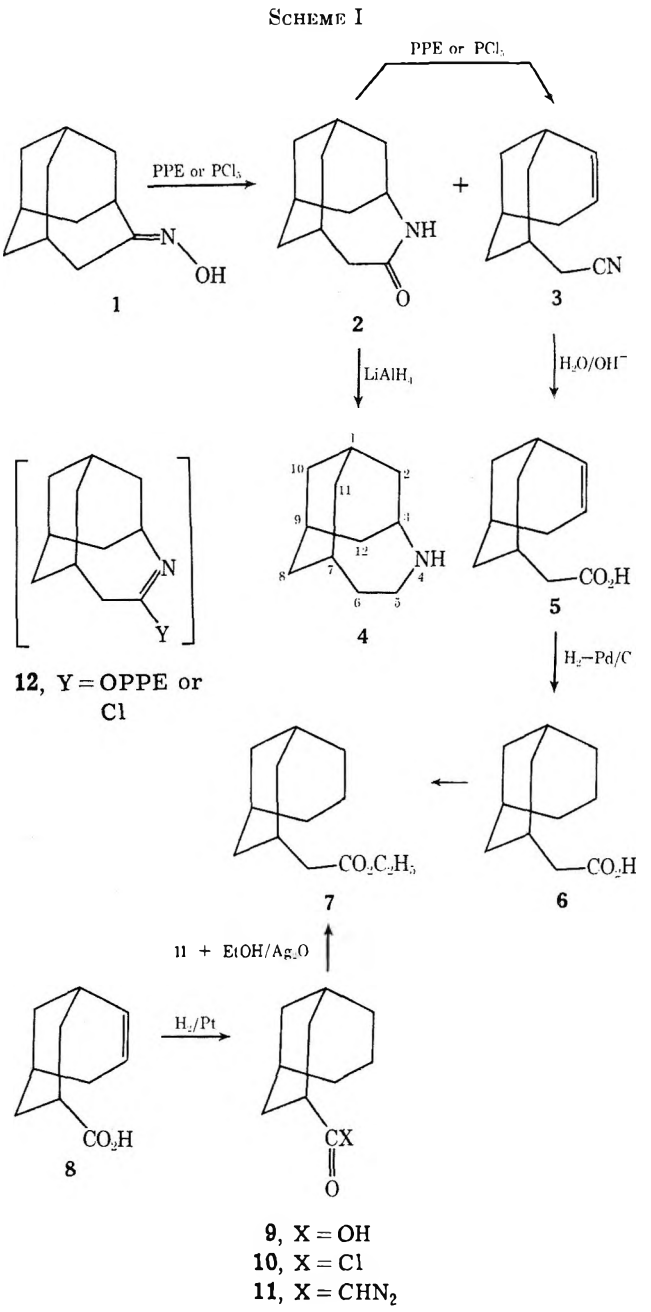



TABLE I

BECKMANN REARRANGMENT OF 1 UNDER VARIOUS CONDITIONS

| Catalyst (mol ratio) | Solvent | Reaction temp, °C | Reaction time, hr | Products,[a] —%— 2 | 3 | Recovered,[a] % 1 |
|---|---|---|---|---|---|---|
| PPE (large excess) | $CHCl_3$ | Reflux | 0.5 | 21[b] | 64[b] | 0 |
| PPE (large excess) | $CHCl_3$ | Reflux | 1 | 0 | 79[b] | 0 |
| $PCl_5$ (2.4) | $Et_2O$ | Room temp | 48 | 83 | 17 | Trace |
| $PCl_5$ (4) | $CHCl_3$ | Room temp | 15 | 64 | 0 | 36 |
| HCl (39) | $CH_3CN$ | 80 | 2 | 56 | 0 | 44 |
| TsCl (1) | DMF | Room temp | 20 | 83 | 0 | 17 |

[a] Glpc analysis. [b] Isolated yield.

(2) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **36**, 2454 (1971).
(3) J. G. Korsloot, V. G. Keizer, and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **88**, 447 (1969).
(4) V. L. Narayanan and L. Setescak, *J. Heterocycl. Chem.*, **6**, 445 (1969).
(5) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969).
(6) T. Sasaki, S. Eguchi, and T. Toru, *J. Org Chem.*, **35**, 4109 (1970).
(7) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).
(8) For the calculated total strain energies of the related carbocyclic ring systems, see footnote 25 in ref 1 and footnote 13 in ref 2.
(9) This is compatible with our previous postulation that the homoadamantan-4-one system rearranges normally in the Beckmann and the Schmidt reactions.

The facile formation of **3** may be useful for preparation of some bicyclo[3.3.1]nonane derivatives and possibly of some homoadamantane derivatives.[10]

### Experimental Section[11]

**Beckmann Rearrangement of *anti*-Homoadamantan-4-one Oxime (1) with PPE.**—The reaction was carried out similarly to the reported procedure[2] but by using a large excess of PPE. A mixture of 1 (900 mg, 5.02 mmol) and PPE (18 g) in chloroform (5 ml) was refluxed for 0.5 hr and the cooled mixture was poured onto ice–water (300 ml). The work-up and purification on a silica gel column eluting with chloroform afforded **7-cyanomethylbicyclo[3.3.1]non-2-ene (3)** as the first fraction (518 mg, 64%): mass spectrum *m/e* (rel intensity) 161 (52, $M^+$), 134 (100), and 119 (44).

*Anal.* Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 82.18; H, 9.32; N, 8.50.

The second fraction gave 4-azatricyclo[5.3.1.$1^{3,9}$]dodecan-5-one (**2**) (189 mg, 21%) as colorless crystals, mp 184–185° (lit.[2] mp 184–185°).

**Conversion of 2 to 3. A. With PPE.**—A mixture of **2** (30 mg, 0.16 mmol) and PPE (540 mg) in chloroform (0.2 ml) was heated at 85° for 0.5 hr. Glpc analysis of the crude product after work-up revealed the formation of **3** in over 99% yield.

**B. With $PCl_5$.**—A mixture of **2** (30 mg, 0.16 mmol) and $PCl_5$ (80 mg, 0.38 mmol) in dry ether (5 ml) was stirred for 69 hr at room temperature. The mixture was poured onto ice–water, neutralized with 10% aqueous potassium hydroxide, and extracted with chloroform (3 × 10 ml). Dried ($MgSO_4$) extract was evaporated to give crude product, which was analyzed on glpc to reveal the formation of **3** in 8% yield and the recovery of **2** (92%).

**Reduction of 2 to 4-Azatricyclo[5.3.1.$1^{3,9}$]dodecane (4).**—A mixture of **2** (280 mg, 1.56 mmol) and lithium aluminum hydride (500 mg) in dry tetrahydrofuran (15 ml) was refluxed for 120 hr. Excess reagent was decomposed by adding water to the cooled mixture. The diluted mixture was extracted with ether (5 × 50 ml) and the combined extracts were dried ($Na_2SO_4$) and evaporated to give **4** (242 mg, 94%) which was purified by sublimation: mp 197–199°; ir (KBr) 3430, 2920, 1440, 1260, and 1160 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ 6.0 (s, 1, NH), 6.34 (m, 1, $C_3$ H), 6.6–7.2 (m, 2, $C_5$ methylene), and 7.7–9.0 (m, 15, other ring protons); mass spectrum *m/e* (rel intensity) 165 (100, $M^+$), 164 (64), 150 (50), 136 (27), 122 (54), and 108 (57).

*Anal.* Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.48. Found: C, 79.69; H, 11.56; N, 8.25.

**Hydrolysis of 3.**—A mixture of **3** (600 mg, 3.72 mmol), ethanol (12 ml), potassium hydroxide (12 g), and water (48 ml) was refluxed for 64 hr under nitrogen atmosphere. The cooled mixture was diluted with water (300 ml) and washed with *n*-hexane (3 × 30 ml). The water layer was acidified with 10% hydrochloric acid (pH *ca.* 5) and extracted with chloroform (7 × 50 ml). The combined extracts were dried ($Na_2SO_4$) and evaporated to give **bicyclo[3.3.1]non-6-ene-3-*endo*-acetic acid (5)** as an oil (555 mg, 82.7%): ir (neat) 3400–2500, 1695, and 1640 $cm^{-1}$; nmr ($CCl_4$) $\tau$ −1.79 (s, 1, COOH), 4.42 (m, 2, CH=CH), and 7.5–9.0 (m, 13, other protons); mass spectrum *m/e* (rel intensity) 180 (3.5, $M^+$), 179 (16), 161 (69), 142 (99), 129 (45), and 115 (100).

*Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.60; H, 8.65.

**Hydrogenation of 5.**—A mixture of **5** (550 mg, 3.06 mmol), ethanol (30 ml), and 5% Pd/C (300 mg) was hydrogenated at room temperature under an atmospheric pressure for 13 hr. The catalyst was removed by filtration through Celite and the solvent was evaporated to give **bicyclo[3.3.1]nonan-3-*endo*-acetic acid (6)** (560 mg, 100%) as colorless crystals. Recrystallization from *n*-hexane afforded an analytical sample: mp 83–85.5°; ir (KBr) 3500–2400 and 1695 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ 0.76 (s, 1, COOH), 7.87 (d, $J$ = 7.5 Hz, *ca.* 2, $-CHCH_2COOH$), and 7.6–9.3 (m, 15, other protons); mass spectrum *m/e* (rel intensity) 182 (6, $M^+$), 164 (8), 123 (54), 122 (30), and 44 (100).

*Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.75; H, 9.70.

**Ethyl Bicyclo[3.3.1]nonan-3-*endo*-acetate (7). A. From 6.**—A mixture of **6** (188 mg, 1.03 mmol), ethanol (12 ml), and 47% boron trifluoride etherate (300 mg) was refluxed for 1 day. The cooled mixture was poured onto 5% aqueous sodium carbonate (60 ml) and extracted with ether (5 × 20 ml). The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent gave **7** as an oil (200 mg, 92%): ir (neat) 2920, 1730, and 1160 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ 5.73 (q, $J$ = 7.2 Hz, 2, $CH_2CH_3$), 7.80 (d, $J$ = 7.80 Hz, 2, $CHCH_2COO-$), 8.01 (t, $J$ = 7.2 Hz, 3, $CH_2CH_3$), and 7.7–9.2 (m, 15, other protons); mass spectrum *m/e* (rel intensity) 210 (10, $M^+$), 183 (13), 165 (76), 137 (36), 123 (85), 122 (90), and 95 (100).

*Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.46; H, 10.32.

**B. From Bicyclo[3.3.1]non-6-ene-3-*endo*-carboxylic Acid (8).**—A mixture of **8**[6] (500 mg, 3.01 mmol), ethanol (10 ml), and platinum oxide (100 mg) was hydrogenated under an atmospheric pressure at room temperature for 1 day. The catalyst was removed by filtration through Celite and the solvent was removed to give colorless solid, which was recrystallized from ethanol to afford **bicyclo[3.3.1]nonan-3-*endo*-carboxylic acid (9)** as crystals (450 mg, 90%): mp 132–133°; ir (KBr) 3400–2500 and 1685 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ −1.18 (s, 1, COOH) and 7.2–9.1 (m, 15, other protons).

*Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.45.

To an ice-cooled solution of **9** (200 mg, 1.19 mmol) in dry *n*-hexane (4 ml) was added thionyl chloride (0.3 ml, 4.2 mmol) and the mixture was stirred for 1 day at room temperature. Evaporation of the solvent gave crude acid chloride **10** as an oil, ir (neat) 1800 $cm^{-1}$, which was dissolved in dry ether (7 ml) and treated with an excess ethereal diazomethane for 1 day. Removal of the solvent and the excess diazomethane afforded diazo ketone **11** as a yellowish oil, ir (neat) 2920, 2110, and 1720 $cm^{-1}$. The crude **11** was dissolved in ethanol (12 ml) and precipitates of polymethylene were removed by filtration. To the filtrate was added freshly prepared silver oxide (100 mg) and the mixture was refluxed for 5 min. Silver oxide was removed by filtration and the solvent was removed to leave crude product, which was purified on a silica gel column eluting with chloroform to afford a colorless oil (105 mg). Glpc analysis (3% silicone SE-30 on Varaport 30, at 180°) of this oil indicated the formation of **7**, homoadamantan-4-one, and methyl bicyclo[3.3.1]nonan-3-*endo*-carboxylate in a 63.3:25.4:11.3 ratio.

**Registry No.**—**1**, 26770-89-8; **2**, 29863-86-3; **3**, 36358-19-7; **4**, 33273-76-6; **5**, 36411-20-8; **6**, 36358-21-1; **7**, 36358-22-2; **9**, 19489-18-0.

(10) *Cf.* (a) D. J. Raber, G. J. Kane, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4117 (1970); (b) M. A. McKervey, D. Faulkner, and H. Hamill, *ibid.*, 1971 (1970); (c) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970).

(11) *Cf.* footnote 27 in ref 6.

## Thermal Cycloaddition of Cyanoallene and 1-(*N*-Morpholino)cyclohexene[1]

JOHN E. BALDWIN,* RONALD H. FLEMING,[2] AND DIANE M. SIMMONS

*Department of Chemistry, University of Oregon, Eugene, Oregon 97403*

*Received June 15, 1972*

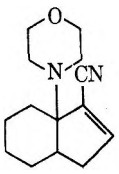
Cyanoallene and 1-(*N*-morpholino)cyclohexene combine thermally to produce a 1:1 adduct, mp 76°, formulated as 1-(*N*-morpholino)-9-cyanobicyclo[4.3.0]non-8-ene, **1**.[3] The morpholino enamine derived from cyclopentanone reacts with cyanoallene to give a similar

(1) Supported by the National Science Foundation and Hoffmann-La Roche Inc.

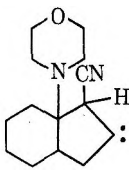
(2) National Science Foundation Trainee, 1968–1972.

(3) W. Ried and W. Käppeler, *Justus Liebigs Ann. Chem.*, **687**, 183 (1965).

cycloadduct, considered to be 1-(*N*-morpholino)-2-cyanobicyclo[3.3.0]oct-2-ene.[3]



1

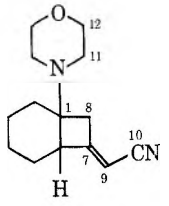


2

The structural assignment **1** for the 1:1 adduct rested on the interpretation of spectral evidence and hydrogenation of the adduct to a saturated nitrile, having the expected (but unreported) nmr spectrum. The mechanism proposed to account for the product assigned involved two-step addition of enamine to cyanoallene in a 1,3 sense to generate a carbene intermediate (**2**), which rearranged through a C–H insertion to afford **1**.

Our concern with allene–olefin cycloadditions[4] led us to reinvestigate the reaction between 1-(*N*-morpholino)-cyclohexene and cyanoallene, for, if the structural assignment **1** were indeed correct, thorough mechanistic scrutiny and numerous synthetic applications would be warranted.

Our study has shown, however, that the 1:1 adduct previously depicted as **1** should be re-formulated as the (2 + 2) cycloaddition product 1-(*N*-morpholino)-(*E*)-7-cyanomethylene-*cis*-bicyclo[4.2.0]octane (**3**).



3

The compound in question was synthesized according to the procedure of Ried and Käppeler.[3] The vinyl proton nmr absorption centered at $\delta$ 5.23 appeared as a quartet of lines, $J$ = 2.2 Hz, with intensities in a 1:3:3:1 ratio, consistent with the vinyl hydrogen being coupled with equal or approximately equal constants to three allylic protons. The pattern is in all respects similar to those we have observed for the isomers of 1-ethylidene-2-methylcyclobutane,[5] and cannot be reconciled with structure **1**. The earlier report[3] described the vinyl resonance as a four-line pattern constituting a doublet of doublets centered at $\delta$ 5.15.

The natural abundance $^{13}C$ nmr spectrum of the cycloaddition product was obtained with broad-band proton decoupling and with no decoupling. The data and the assignments made are given in Table I.

It has been established for cyano-substituted ethylenes that the $\beta$-carbon resonance is shifted downfield, whereas the $\alpha$-carbon resonance is shifted upfield.[6] Opposite behavior is observed for alkyl-substituted ethylenes.[6] Taken together, these two effects should cause the vinyl carbon singlet of structure **1** to occur upfield from the vinyl carbon doublet. On the other hand, the vinyl doublet of structure **3** would be expected substantially upfield from the singlet, in accord with the experimental data.

TABLE I

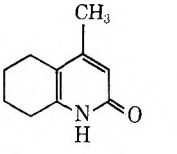
NATURAL ABUNDANCE $^{13}C$ NMR SPECTRUM OF ADDUCT **3**

| Chem shift[a] | Multiplicity | $J^{13}C-H$, Hz[b] | Assignment |
|---|---|---|---|
| −90.2 | s | | C-7 |
| −38.4 | s | | C-10 |
| −12.7 | d | 175 | C-9 |
| 10.3 | t | 143 | C-12 |
| 20.1 | s | | C-1 |
| 29.0 | d | 133 | C-6 |
| 31.2 | t | 133 | C-11 |
| 33.8 | t | 138 | C-8 |
| 50.8 | t | 130 | C-2,3,4,5 |
| 53.5 | t | 128 | C-2,3,4,5 |
| 55.1 | t | 128 | C-2,3,4,5 |
| 57.0 | t | 128 | C-2,3,4,5 |

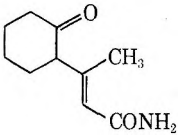
[a] Values given in ppm from deuteriochloroform as internal standard and solvent. [b] Coupling constants are given only for those protons attached directly to the carbon in question.

The nmr spectral data indicate the 1:1 adduct is a single isomer. The cis geometry for the bicyclic ring system is assigned primarily on grounds of mechanistic plausibility; the *E* configuration for the cyanomethylene function is suggested tentatively, for it seems in better accord with the $^{13}C$ chemical shifts.

Further confirmation of structure **3** was obtained by chemical correlation with a known compound. Treatment of the adduct **3** with mild base leads to a white crystalline solid identified as 4-methyl-5,6,7,8-tetrahydrocarbostyril (**4**) through direct comparisons with an authentic sample prepared by the method of Sakurai and Midorikawa.[7]



4



5

Formation of the tetrahydrocarbostyril **4** from **3** under these conditions is easily rationalized as proceeding through intermediates such as **5** derivable through simple hydrolysis; no change in the carbon skeleton is involved in the **3** → **4** conversion. By contrast, the transformation **1** → **4** would be awkward to formulate in straightforward terms.

Thus we conclude on the basis of proton and carbon nmr data, and of a chemical correlation, that the 1-(*N*-morpholino)cyclohexene cycloadduct with cyanoallene should be assigned structure **3**, not **1**,[3] and the cycloaddition process itself presents no unique mechanistic problems.

### Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Proton and carbon nmr spectra were measured with a Varian XL-100-FT spectrometer acquired through NSF and NIH-HSAA grants to the University of Oregon. The mass

(4) J. E. Baldwin and R. H. Fleming, *Fortschr. Chem. Forsch.*, **15**, 281 (1970).

(5) J. E. Baldwin and R. H. Fleming, *J. Amer. Chem. Soc.*, **94**, 2140 (1972).

(6) G. B. Savitsky, P. D. Ellis, K. Namikawa, and G. E. Maciel, *J. Chem. Phys.*, **49**, 2395 (1968).

(7) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jap.*, **41**, 165 (1968).

spectrum was determined on a CEC-110-21B spectrometer by Dr. Susan Rottschaefer.

**4-Methyl-5,6,7,8-tetrahydrocarbostyril (4).**—Sodium carbonate (100 mg, 0.94 mmol), adduct **3** (201 mg, 0.865 mmol), and 80% ethanol (5 ml) were heated at reflux for 1 hr. Chloroform (20 ml) was added, and the mixture was washed with water (2 × 20 ml) and brine (1 × 20 ml), dried ($MgSO_4$), filtered, and concentrated to yield 127 mg of solid residue (about 60% **4** by nmr). Recrystallization from acetone gave 30.8 mg (22%) of compound **4**. A portion after further purification by recrystallization from chloroform had mp 256°: nmr ($CDCl_3$) broad signal δ 12.76 (1 H), singlet 6.26 (1 H), broad signal 2.68 (2 H), broad signal 2.39 (2 H), singlet 2.11 (3 H), complex multiplet 1.77 (4 H); mass spectrum *m/e* (rel intensity) 163 (100), 148 (10), 135 (42), 107 (47). The compound was identical with an authentic sample of 4-methyl-5,6,7,8-tetrahydrocarbostyril as judged by nmr spectral, melting point, and mixture melting point criteria.

**Registry No.**—**3**, 36286-99-4; **4**, 36287-00-0; cyanoallene, 1001-56-5; 1-(*N*-morpholino)cyclohexene, 670-80-4.

## Electron Impact Induced Fragmentations Mimicking Retro-1,3-dipolar Cycloadditions

STEEN HAMMERUM* AND PEDER WOLKOFF

*Department of General and Organic Chemistry, The H. C. Ørsted Institute, The University of Copenhagen, Universitetsparken 5, DK-2100, Copenhagen, Denmark*

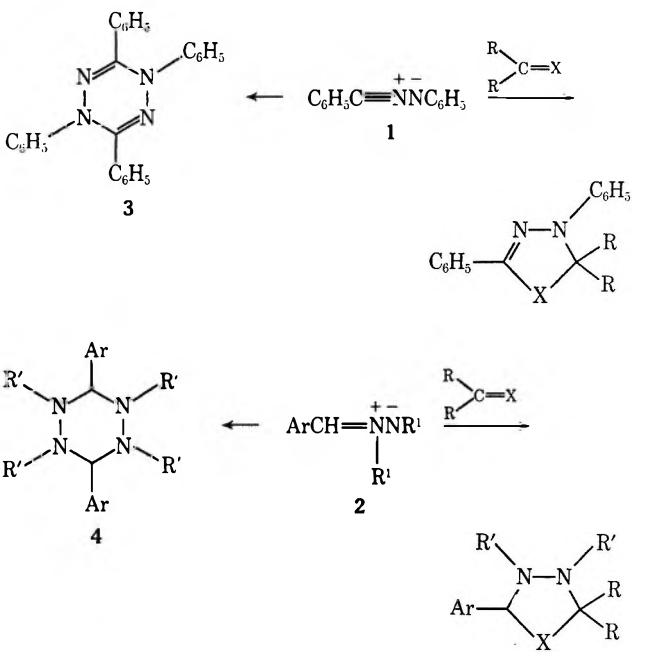
*Received June 6, 1972*

Correlation of thermal and photochemical processes with reactions that occur after electron impact has received considerable attention. The best known examples of successful analogies are the similarity of the mass spectrometric McLafferty rearrangement–decomposition process and the Norrish type 2 photofragmentation, and the occurrence of thermal, photochemical, and mass spectrometric retro-Diels–Alder reactions.[1] Recently, Nomura, Furusaki, and Takeushi[2] have proposed that retro-1,3-dipolar cycloadditions also have mass spectrometric counterparts, since 4- and 5-aminoisoxazolidines formed by 1,3-dipolar cycloaddition of enamines to nitrones yield ionized enamines upon electron impact. Earlier, at least one other well-established mass spectrometric retro-1,3-dipolar cycloaddition has been reported,[3] namely, the elimination of *tert*-butyl isocyanide from the molecular ion of the 3-(*N*-*tert*-butylimino)-1,2-diazetidine formed by addition of *N*-(*p*-nitrophenylimino)-1,2,3,4-tetrahydroisoquinoline to *tert*-butyl isocyanide.

We wish here to report the preliminary results of an investigation of the mass spectrometric behavior of heterocyclic compounds formed by 1,3-dipolar cycloaddition reactions of nitrile imines and azomethine imines, to show that such compounds upon electron impact may fragment by way of a cycloelimination reaction corresponding, formally, to the reverse process of their formation.

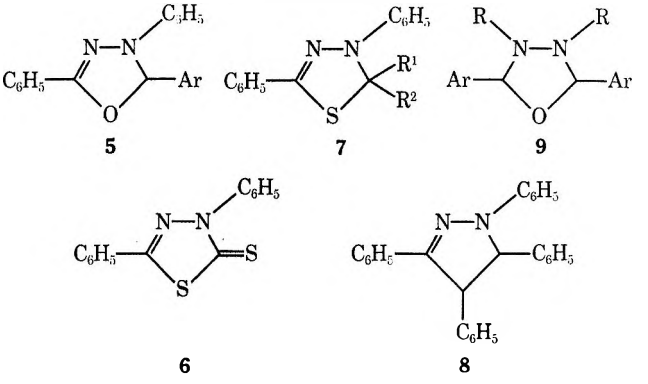
Addition of compounds incorporating C=C, C=O, or C=S double bonds to diphenylnitrileimine (**1**) or azomethine imines (**2**) usually yields five-membered ring compounds,[4] as illustrated in Scheme I.

SCHEME I



In the absence of dipolarophiles the 1,3-dipolar species dimerize to give dihydro-1,2,4,5-tetrazines (**3**) or hexahydro-1,2,3,4-tetrazines (**4**).[4] We have examined the mass spectra of several compounds formed in such reactions, **3**–**9**[5] (Scheme II).

SCHEME II



The mass spectrometric decomposition of the five-membered ring compounds **5**–**8** leads in all cases to ions corresponding in elemental composition to the parent 1,3 dipole (**1**, *m/e* 194), usually accompanied by minor peaks corresponding to the ionized dipolarophile. The most pronounced example of such retro-1,3-dipolar cycloaddition is found in the fragmentation of **5**, where more than 60% of $\Sigma_{50}$ is carried by the three ions shown in Scheme III. Metastable ion peaks corresponding to both processes are observed in the spectra and have also been observed by metastable

(1) T. W. Bentley and R. A. W. Johnstone, *Advan. Phys. Org. Chem.*, **8**, 151 (1970), and references cited therein.

(2) Y. Nomura, F. Furusaki, and Y. Takeushi, *J. Org. Chem.*, **37**, 502 (1972).

(3) J. A. Deyrup, *Tetrahedron Lett.*, 2191 (1971).

(4) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

(5) Formulas **4**, **5**, **7**, and **9** each represent several compounds of the class in question. A full discussion of the mass spectra of these compounds will appear elsewhere.

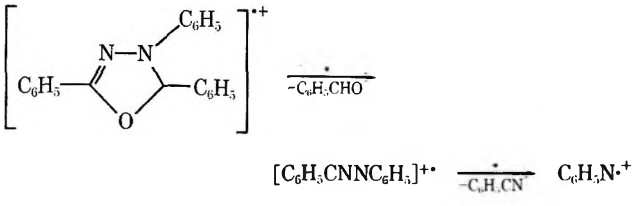
TABLE I

INTENSITIES OF PEAKS CORRESPONDING TO IONIZED DIPOLE AND DIPOLAROPHILE IN MASS SPECTRA OF REPRESENTATIVE 1,3-DIPOLAR CYCLOADDUCTS

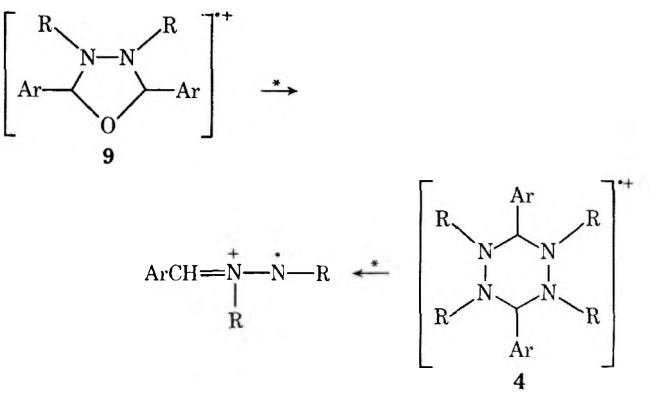
| Registry no. | Compd | Dipole[a] | Dipolarophile[a] | Base peak |
|---|---|---|---|---|
| 36411-19-5 | **4**, Ar = *p*-$CH_3OC_6H_4$; R′ = $CH_2CH_3$ | 206 (42)[b] | 206 (42)[b] | $C_8H_9O$ |
| 36358-04-0 | **4**, Ar = 3-pyridyl; R′ = $CH_3$ | 149 (25)[c] | 149 (25)[c] | $C_7H_8N_2$ |
| 20561-17-5 | **5**, Ar = $C_6H_5$ | 194 (48) | 106 (2) | $C_6H_5N$ |
| 36358-06-2 | **5**, Ar = *p*-$CH_3OC_6H_4$ | 194 (57) | 136 (2) | $C_6H_5N$ |
| 36358-07-3 | **7**, $R^1$ = H; $R^2$ = H | 194 (5) | 46 (2) | $M\cdot^+$ |
| 36358-08-4 | **7**, $R^1$ = $CH_2CH_3$; $R^2$ = H | 194 (10) | 74 (3) | $[M^+ - H_2]$[d] |
| 13187-62-7 | **7**, $R^1$ = $C_6H_5$; $R^2$ = H | 194 (26) | 122 (2) | $C_6H_5N$ |
| 36358-10-8 | **7**, $R^1$ = $C_6H_5$; $R^2$ = $C_6H_5$ | 194 (41) | 198 (1) | $C_{13}H_{10}N$ |
| 36358-11-9 | **7**, $R^1$ = $C_6H_5$; $R^2$ = $N(CH_2)_5$ | 194 (82) | 205 (7) | $C_6H_5N$ |
| 36358-12-0 | **7**, $R^1$ = *p*-$CH_3OC_6H_4$; $R^2$ = $OCH_2CH_3$ | 194 (98) | 196 (3) | $C_6H_5N$ |
| 36358-13-1 | **9**, Ar = *m*-$NO_2C_6H_4$; R = $CH_2CH_3$ | 221 (56) | 151 (100) | $C_7H_5NO_3$ |

[a] *m/e* (rel intensity). [b] 205 (72). [c] 148 (94). [d] Possibly of thermal origin.

SCHEME III



SCHEME IV



defocusing, showing that the *m/e* 194 ion is not of thermal origin. Furthermore, the intensity ratio $M\cdot^+$ to *m/e* 194 does not change significantly when the temperature of the ion source is raised from 100 to 250°.

The mass spectrum of **6** likewise exhibits strong peaks corresponding to the fragment ions shown in Scheme III, whereas these are formed in lesser abundance in the decomposition of **7** and **8**. The intensity of the peaks corresponding to ionized **1** in the spectra of the various thiadiazolines **7** examined varies with $R^1$ and $R^2$, and is more intense when the eliminated fragment is aromatic (*cf.* Table I). This indicates that the retro-1,3-dipolar cycloaddition reaction within a class of compounds is dependent upon the stability of the eliminated neutral.

The retro-1,3-dipolar cycloaddition reaction occurs in compounds **5**–**7** principally with charge retention in the fragment corresponding to the dipolar species, while the ionized dipolarophiles only give rise to peaks of negligible intensity; only compound **8** produces ions of about equal abundance corresponding to **1** and to stilbene. These results contrast with the earlier suggestion of Nomura, Furusaki, and Takeushi[2] that this kind of cycloreversion reactions will proceed with charge retention mainly in the dipolarophile fragment.

The fragmentations of the cycloadducts of azomethine imines, **4** and **9** (Scheme IV), also give evidence of mass spectrometric retro-1,3-dipolar cycloadditions. The five-membered ring compounds **9** decompose to give abundant ions corresponding in elemental composition to azomethine imine as well as aldehyde, the latter producing the base peaks of the spectra.

Hexahydro-1,2,4,5-tetrazines **4** similarly produce ions corresponding in elemental composition to azomethine imines by bisection of the ring; this reaction is frequently accompanied by hydrogen transfer reactions leading to abundant ions 1 amu less (*cf.* Table I). The azomethine imine ions formed from **4** and **9** decompose further by nearly identical fragmentations, indicating these ions to be of similar structure. Hexahydro-1,2,4,5-tetrazines formed in reactions other than cyclodimerization of azomethine imines also undergo facile bisection of the ring to give abundant ions of half the mass of the molecular ion; these ions may likewise be regarded as ionized azomethine imines.[6]

Dihydro-1,2,4,5-tetrazines, however, fragment differently; the mass spectrum of **3** exhibits only a weak peak corresponding to ionized **1**. Instead [6 → 4 + 2][7] fragmentation reactions produce $PhCNPh^+$ and $PhCN\cdot^+$ ions. Similar [6 → 4 + 2] reactions are also of importance in the decomposition of **4**, leading to $ArCH{=}NR\cdot^+$ ions. This shows that mass spectrometric cycloreversion reactions formally resembling retro-1,3-dipolar cycloadditions are not always important in the decomposition of 1,3-dipolar cycloadducts. However, such reactions are expected to occur frequently among the mass spectrometric decomposition reactions of many compounds that may be formed through 1,3-dipolar cycloadditions.

(6) (a) S. Hammerum and J. Møller, *Org. Mass Spectrom.*, **5**, 1209 (1971). (b) W. Sucrow, H. Bethke, and G. Chondromatidis, *Tetrahedron Lett.*, 1481 (1971). (c) J. H. Cooley and J. W. Atchison, *ibid.*, 4449 (1969). (d) The M/2 ions formed in the fragmentation of 1,4-disubstituted hexahydro-1,2,4,5-tetrazines are probably an exception, since rearrangement by hydrogen migration to the isomeric hydrazone structure appears to be favored (ref 6a); the facile thermal dissociation of these compounds to give hydrazones (ref 6a,b,e) complicates an assignment of structure to the fragment ions of the same elemental composition. Evidence for similar rearrangements is not found in the mass spectra of other hexahydro-1,2,4,5-tetrazines. (e) S. R. Johns, J. A. Lamberton, and E. R. Nelson, *Aust. J. Chem.*, **24**, 1859 (1971).

(7) Simple cleavage of two ring bonds in a six-membered ring to give fragments containing, respectively, four and two ring atoms.

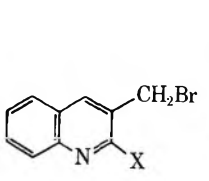
## Benzylic Halogenation of Methylquinolines

ROBERT E. LYLE,* DAVID E. PORTLOCK, MICHAEL J. KANE, AND JAMES A. BRISTOL[1]

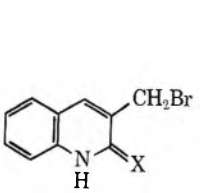
*Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824*

*Received May 10, 1972*

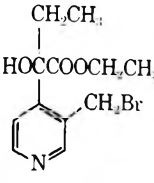
Benzylic halogenation by *N*-bromosuccinimide is a standard method of synthesis of bromomethyl aromatic compounds.[2] Thus, when a 2-substituted 3-bromomethylquinoline (**1**) and a 4-substituted 3-bromomethylpyridine (**2**) were needed for a synthetic approach[3a] to camptothecin,[3b] it was assumed that this reaction could be used with the corresponding methyl heterocycle. A literature survey described such halogenations of 2- and 4-methyl nitrogen heterocycles;[4] however, there was a disturbing lack of information about 3-methyl derivatives. Direct halogenation of 3-methylquinoline and β-picoline was reported to be unsuccessful.[5]



**1**, X = H, halogen



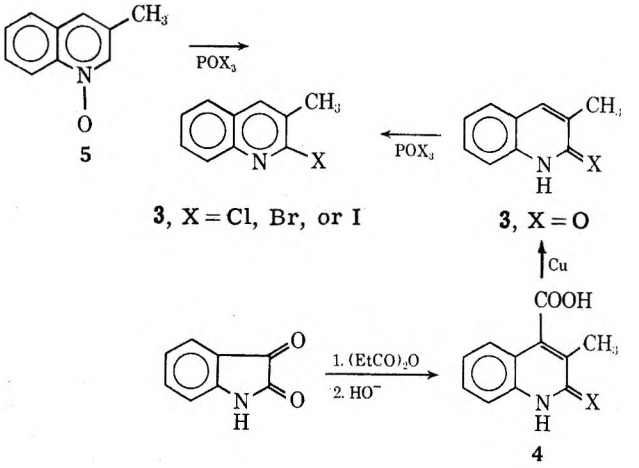
**1**, X = O



**2**

The halogenation of the 4-substituted β-picoline, β-picoline, and 3-methylquinoline gave no 3-bromomethyl derivative on treatment with a variety of bromination conditions. In each reaction it was evident that a salt was formed and apparently the salt failed to undergo benzylic halogenation. On this basis the preparation of **1** was attempted by benzylic halogenation of 2-halo-3-methylquinoline, since the 2-halo substituent should decrease the basicity of the nitrogen heterocycle and interfere with salt formation.[6]

The 2-halo-3-methylquinoline **3** was prepared by rearrangement of 3-methylquinoline 1-oxide[7] (**5**) or from the 3-methyl-2-quinoline prepared by the Pfitzinger reaction.[8-10] The 2-chloro and 2-bromo derivatives of **3** were prepared by using the appropriate phosphorus oxyhalide, and the 2-iodo derivative was



**5**

**3**, X = Cl, Br, or I

**3**, X = O

**4**

prepared from the 2-chloro derivative by halogen exchange using sodium iodide in methyl ethyl ketone.

The halogenations of all the 2-substituted 3-methylquinolines (**3**, X = Cl, Br, I, or O) with *N*-bromosuccinimide were successful, giving good yields of 3-bromomethyl 2-substituted quinolines (**1**). These results strongly suggest that the decreased basicity of **3** (X = halogen or O) as compared with **3** (X = H) is necessary to allow successful benzylic bromination.

### Experimental Section[11]

**2-Hydroxy-3-methylcinchoninic Acid** (**4**).—A mixture of 500 g (3.4 mol) of isatin and 885 g (6.8 mol) of propionic anhydride was stirred mechanically and heated under reflux for 2.5 hr. After this time the resulting orange solution was allowed to cool to room temperature and the solid was removed by filtration and washed well with ether. After drying, 556 g (81%) of 1-propionyl isatin, mp 140–141°, was obtained.

To a mechanically stirred mixture of 221 g (1.09 mol) of unpurified 1-propionylisatin in 3000 ml of water was added 90 g (2.25 mol) of sodium hydroxide pellets. The mixture was heated to boiling for 1 hr and subsequently charcoaled with 15 g of Norit A. After 10 min the mixture was filtered through Celite to afford a light yellow solution that was neutralized with 550 ml of 6 *N* HCl with mechanical stirring. The resultant yellow solid was removed by filtration, washed well with cold water, and then dried to constant weight at 100°. The bright yellow powder, **4**, mp 321–323° (lit.[8] mp 315–217°), weighed 103 g (46% conversion). From the filtrate was obtained 67 g of isatin, mp 204–205° (lit.[12] mp 197–200°). The yield of **4** based on consumed isatin was 81%.

**3-Methyl-2-quinolone** (**3**, X = O).—A mixture of 30 g (0.148 mol) of **4**, 6 g (0.094 mol) of copper powder, and 100 g of freshly distilled quinoline was stirred and heated for 5 hr at 235°. After this time 65 g of quinoline were removed by distillation, and on cooling crude **3** (X = O) precipitated. The solid was washed with petroleum ether (bp 30–60°), treated with Norit in isopropyl alcohol solution, and recrystallized from isopropyl alcohol to give 16 g (68%) of 3-methyl-2-quinolone (**3**, X = O), mp 238–240° (lit.[9] mp 234–235°).

**2-Chloro-3-methylquinoline** (**3**, X = Cl).—A mixture of 5.00 g (0.031 mol) of **3** (X = O) and 100 ml of phosphorus oxychloride ($POCl_3$) was stirred and heated under reflux for 2 hr. The hot reaction mixture was then slowly poured with stirring onto 400 g of crushed ice. The mixture was extracted with methylene chloride and this extract was dried over anhydrous $K_2CO_3$. After filtration and concentration, a red-brown oil was obtained which solidified upon cooling, and after recrystallization from hexane gave 4.9 g (88%) of **3** (X = Cl) as white crystals, mp 83–84° (lit.[9] mp 89–90°).

**2-Chloro-3-methylquinoline** (**3**, X = Cl).—To 200 ml of $POCl_3$ cooled in an ice bath was added 20.0 g (0.126 mol) of 3-methyl-

(1) NDEA Title IV Fellow, 1969–1971; UNH Dissertation Year Fellow, 1971–1972.

(2) W. Forest (Ed.), "New Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 151.

(3) (a) The general approach to the total synthesis of camptothecin was reported at the International Union of Pure and Applied Chemistry Meeting, Boston, Mass., Abstracts, XXII IUPAC, 1971, No. 163. (b) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. H. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).

(4) (a) B. R. Brown, D. L. Hammick, B. H. Thewlis, and P. J. Wolbridge, *J. Chem. Soc.*, 1369 (1953), and references cited therein; (b) M. Hasegawa, *Chem. Pharm. Bull.*, **1**, 47, 293 (1953); (c) B. Prijs, R. Gall, R. Hinderling, and H. Erlenmeyer, *Helv. Chim. Acta*, **37**, 90 (1954); (d) B. D. Mookherjee and E. M. Klaiber, *J. Org. Chem.*, **37**, 511 (1972).

(5) B. R. Brown, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145 (1951).

(6) P. T. Sullivan and S. J. Norton, *J. Med. Chem.*, **14**, 557 (1971).

(7) For example, see J. K. Lindquist, *J. Chem. Soc.*, 2816 (1953).

(8) H. Meyer, *Monatsh. Chem.*, **26**, 1322 (1905).

(9) G. Ornstein, *Chem. Ber.*, **40**, 1088 (1907).

(10) T. L. Jacobs, S. Winstein, G. B. Linden, J. H. Robson, E. F. Levy, and D. Seymour, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1956, p 456.

(11) All melting points were taken with a Mel-Temp apparatus and are uncorrected.

(12) C. S. Marvel and G. S. Hien, *Org. Syn.*, **5**, 71 (1925).

quinoline *N*-oxide[13] cautiously. The mixture was then heated under reflux for 15 min and poured slowly over crushed ice. The mixture was made strongly basic with a KOH solution. The aqueous layer was extracted with ether, and the ether extracts were dried ($K_2CO_3$) and concentrated to give a brown solid. This solid was dissolved in low-boiling petroleum ether and basic alumina was added. Stirring for 10 min followed by filtration gave a yellow filtrate which upon concentration gave 17.3 g (78%) of crude 2-chloro-3-methylquinoline (**3**, X = Cl). Recrystallization from hexane gave white needles, mp 82–84° (lit.[9] mp 89–90°).

**2-Bromo-3-methylquinoline (3, X = Br).**—A mixture of 5.00 g (0.031 mol) of **3** (X = O) and 12.70 g (0.045 mol) of phosphorus oxybromide was stirred at 140° for 3 hr. After this time the mixture was poured onto 200 g of crushed ice and subsequently extracted with both 600 ml of methylene chloride and water. When solution was complete, the layers were separated and the aqueous layer was extracted with 150 ml of methylene chloride. The combined organic layers were washed with 150 ml of water, dried ($MgSO_4$), filtered, and concentrated to yield **3** (X = Br) as a tan solid that weighed, after drying, 5.78 g (83%). The solid was recrystallized once from hexane to afford an analytical sample that melted at 96–97°: pmr ($CF_3COOH$) δ 8.42 (s, 1 H, 4-quin), 7.87–8.33 (m, 4 H, ArH), and 2.52 ppm (s, 3 H, $CH_3$).

*Anal.* Calcd for $C_{10}H_8BrN$: C, 54.07; H, 3.64; N, 6.31. Found: C, 54.41; H, 3.58; N, 6.36.

**2-Chloro-3-methylquinoline Hydrochloride (3, X = Cl·HCl).**—2-Chloro-3-methylquinoline (**3**, X = Cl) was taken up in ether and anhydrous HCl was bubbled into the solution until precipitation was complete. The solid was removed by filtration and dried to give **3** (X = Cl) hydrochloride: mp 215–218°; pmr ($CDCl_3$) δ 8.99 (s, 1 H, 4-quin), 9.63–7.61 (m, 4 H, ArH), and 2.74 ppm (s, 3 H, $CH_3$).

*Anal.* Calcd for $C_{10}H_9Cl_2N$: C, 56.11; H, 4.24; N, 6.54. Found: C, 56.34; H, 4.05; N, 6.61.

**2-Iodo-3-methylquinoline (3, X = I).**—To a stirred mixture of 24.0 g (0.112 mol) of **3** (X = Cl, HCl) in 600 ml of methyl ethyl ketone (MEK) was added 60 ml of a saturated aqueous solution of sodium iodide. The solution was heated under reflux for 24 hr. The solvent was removed by distillation, and excess water was added. The brown solid which precipitated was treated with saturated aqueous sodium bicarbonate and ether. The aqueous layer was extracted with chloroform and the combined organic phases were washed with aqueous sodium bisulfite, dried ($MgSO_4$), filtered, and concentrated to yield a light red oil that solidified upon the addition of hexane. Recrystallization of the solid from hexane gave 19.4 g (60%) of **3** (X = I) as long needles, mp 87–89°, pmr ($CH_2Cl_2$) δ 7.88–7.25 (m, 5 H, ArH) and 2.52 ppm (s, 3 H, $CH_3$).

*Anal.* Calcd for $C_{10}H_8IN$: C, 44.64; H, 3.00; N, 5.21. Found: C, 44.56; H, 2.82; N, 5.13.

**2-Chloro-3-bromomethylquinoline (1, X = Cl).**—To a solution of 14.7 g (0.082 mol) of **3** (X = Cl) in 300 ml of dry $CCl_4$ was added 14.8 g (0.082 mol) of *N*-bromosuccinimide (NBS) along with 0.1 g of dibenzoyl peroxide. The mixture was heated with a 100-W lamp and reflux was continued for 11 hr. After this time the mixture was filtered, and the solvent was evaporated to afford 20.0 g (95%) of a white solid, which on recrystallization from hexane gave **1** (X = Cl) as white needles, mp 121–125°, pmr ($CDCl_3$) δ 8.21–7.54 (m, 5 H, quin) and 4.69 ppm (s, 2 H, $CH_2$).

*Anal.* Calcd for $C_{10}H_7BrClN$: C, 46.83; H, 2.75; N, 5.46. Found: C, 46.82; H, 2.90; N, 5.42.

**2-Bromo-3-bromomethylquinoline (1, X = Br).**—Using the procedure above, 14.22 g (0.064 mol) of **3** (X = Br) and 11.39 g (0.064 mol) of NBS gave 18.65 g (93%) of **1** (X = Br), mp 136–138°, pmr ($CDCl_3$) δ 8.50–7.48 (m, 5 H, ArH) and 4.91 ppm (s, 2 H, $CH_2$).

*Anal.* Calcd for $C_{10}H_7Br_2N$: C, 39.90; H, 2.35; N, 4.65. Found: C, 40.20; H, 2.27; N, 4.83.

**2-Iodo-3-bromomethylquinoline (1, X = I).**—The method above was used to convert 19.4 g (0.072 mol) of **3** (X = I) and 13.3 g (0.072 mol) of NBS to 11.0 g (45%) of **1** (X = I), mp 125–128°, pmr ($CDCl_3$) δ 8.32–7.56 (m, 5 H, quin) and 4.72 ppm (s, 2 H, $CH_2$).

*Anal.* Calcd for $C_{10}H_7BrIN$: C, 34.52; H, 2.03; N, 4.02. Found: C, 34.82; H, 2.03; N, 3.89.

(13) O. Buchardt, J. Becker, and C. Lohse, *Acta Chem. Scand.*, **19**, 1120 (1965).

**3-Bromomethyl-2-quinolone (1, X = O).**—The method above converted 5.0 g (0.031 mol) of **3** (X = O) and 5.6 g (0.031 mol) of NBS to 5.4 g (72%) of **1** (X = O), mp 218–219°, pmr ($CF_3COOH$) δ 8.72–7.68 (m, 4 H, quin) and 4.74 ppm (s, 2 H, $CH_2$).

*Anal.* Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.38; N, 5.88. Found: C, 50.17; H, 3.34; N, 5.85.

**Registry No.**—**1** (X = Cl), 35740-82-0; **1** (X = Br), 35740-83-1; **1** (X = I), 35740-84-2; **1** (X = O), 35740-85-3; **3** (X = Br), 35740-86-4; **3** (X = Cl) HCl, 35740-87-5; **3** (X = I), 35820-73-6; 1-propionylisatin, 17529-69-0.

**Acknowledgment.**—This research was supported in part by Grant CA-12149-01 from the National Cancer Institute of the National Institutes of Health. The authors express their appreciation for this help.

## Tetraalkylammonium Trifluoromethanesulfonates as Supporting Electrolytes[1]

K. Rousseau,[2] G. C. Farrington,[2] and D. Dolphin*

*Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138*

*Received May 21, 1972*

The renewed interest in synthetic organic electrochemistry is derived in part from the increased use of nonaqueous and, in particular, aprotic solvents. The use of such solvents is limited, however, by the availability of supporting electrolytes which ionize to give solutions of sufficiently low resistance. This becomes particularly important in bulk electrolyses in which a high solution resistance results in the generation of considerable heat.

Among the most widely used supporting electrolytes in solvents such as acetonitrile, dimethylformamide, methylene dichloride, and tetrahydrofuran are the tetraalkylammonium salts. Their ready availability, ease of purification, and the potential range over which they can be used makes them ideally suited for a variety of electrochemical uses. While the cation determines the solubility, the choice of a specific tetraalkylammonium salt is governed principally by the chemistry of the anion. Unfortunately, the choice of anions is limited. The ease of oxidation of halides to the corresponding halogens, coupled with the high nucleophilicity of the halide ion, severely limits their use as supporting electrolytes. Acetates have been suggested as useful supporting electrolytes, since upon oxidation only ethane and carbon dioxide are generated (*via* the Kolbe reaction). However, it was not found possible to prepare tetraalkylammonium acetates free of acetic acid. House[3] has come to the conclusion that the tetraalkylammonium fluoroborates are the supporting electrolytes of choice, since they are readily prepared and purified, and exhibit the necessary electrochemical properties. Thus, the tetra-*n*-butylammonium salt shows a limiting reduction potential (at mercury) more cathodic than 2.7 V (all potentials are quoted against the sat-

(1) This work was supported by the National Institutes of Health (Grant AM 14343).

(2) NIH Predoctoral Fellow.

(3) H. O. House, E. Feng, and N. P. Peet, *J. Org. Chem.*, **36**, 2371 (1971).

TABLE I
SOLUBILITIES OF TETRAALKYLAMMONIUM SALTS[b]

| | | DMF | | $CH_3CN$ | | $CH_2Cl_2$ | | THF | |
|---|---|---|---|---|---|---|---|---|---|
| | $CF_3SO_3^-$ | 7.2 | (2.58) | 8.6 | (3.1) | 8.5 | (3.0) | 0.2 | (0.08) |
| $Et_4N^+$ | $ClO_4^-$[a] | 2.3 | (1.00) | 2.6 | (1.13) | | | | (<0.01) |
| | $BF_4^-$[a] | 2.7 | (1.24) | 3.7 | (1.69) | | | | (<0.01) |
| | $CF_3SO_3^-$ | 4.9 | (1.49) | 5.0 | (1.49) | 4.9 | (1.46) | ~0.1 | (0.03) |
| *n*-$Pr_4N^+$ | $ClO_4^-$[a] | 2.1 | (0.74) | 2.1 | (0.74) | | | | (<0.01) |
| | $BF_4^-$[a] | 3.2 | (1.17) | 3.6 | (1.32) | | | | (<0.01) |
| | $CF_3SO_3^-$ | 8.8 | (2.25) | 9.8 | (2.5) | 9.6 | (2.45) | 9.2 | (2.35) |
| *n*-$Bu_4N^+$ | $ClO_4^-$[a] | 7.9 | (2.29) | 7.0 | (2.05) | | | 5.0 | (1.46) |
| | $BF_4^-$[a] | 7.5 | (2.34) | 7.1 | (2.21) | | | 6.5 | (2.02) |

[a] Reference 3. [b] In g/10 ml (concentration, *M*).

urated calomel electrode unless otherwise stated) in a variety of aprotic solvents and gives solutions with sufficiently low specific resistances to be suitable for bulk electrolyses.

The principal consideration in choosing a supporting electrolyte, once the electrochemical requirements have been met, is one of inertness toward electrochemically produced intermediates and products. In cathodic reductions where anions and anion radicals are likely intermediates it is to be expected that the tetrafluoroborate anion will be inert. However, in anodic oxidations reactions between tetrafluoroborate and electrochemically generated cations and cation radicals are expected. A chemical analogy is that of the Balz–Schiemann reaction[4] in which the thermal decomposition of an aryl diazonium fluoroborate yields the corresponding aryl fluoride *via* the aryl cation. Similarly, we have found that porphyrin $\pi$ dications, which are stable in the presence of tetraalkylammonium perchlorates, react with tetrafluoroborates. Clearly then, the tetrafluoroborates do not meet the criteria of chemical inertness during anodic oxidations. This is also true of most of the other supporting electrolytes currently in use, except for those in which the anion is perchlorate. From an electrochemical viewpoint the tetraalkylammonium perchlorates are ideal. They are readily purified, highly soluble in a wide variety of solvents, and the specific resistances and limiting potentials of the resulting solutions are as favorable as those obtained with any other systems. Perchlorate salts suffer from only one disadvantage: since the perchlorate anion is a powerful oxidizing agent, organic perchlorates are frequently, and unpredictably, explosive! We have prepared a number of organic cations by electrochemical methods and have isolated them as their perchlorate salts. The ever-present dangers of such practices were highlighted when it was reported[5] that a recrystallized sample of tetra-*n*-propylammonium perchlorate exploded upon drying at room temperature!

Such considerations have prompted us to look for a cation which possesses the nonnucleophilic and low coordinating power of perchlorates but lacks its oxidizing properties. Since nucleophilicity is associated with conjugate bases of strong acids, our attention was drawn to trifluoromethanesulfonic acid, the strongest Brønsted acid known.[6] The stability of the trifluoromethanesulfonate anion is illustrated by the observation that methyl trifluoromethanesulfonate is $10^4$ times more reactive toward acetolysis than methyl *p*-toluenesulfonate.[7] Moreover, studies on the trifluoromethanesulfonate anion show it to be a very poor ligand.[8]

Treatment of aqueous solutions of tetraalkylammonium bromides or hydroxides with trifluoromethanesulfonic acid gives a precipitate of the corresponding trifluoromethanesulfonate salt. Recrystallization from a variety of aprotic solvents, followed by drying at elevated temperatures, yields the pure, anhydrous, solvent-free product. The salts have solubilities (Table I) which in every case are comparable to those of the corresponding tetrafluoroborates or perchlorates. Furthermore, the specific resistances of solutions of these salts are very similar (Table II) to those of the perchlorates and tetrafluoroborates. Finally, the limiting anodic and cathodic potentials for the solutions (Table III) are, where they can be compared directly, essentially the same as for the perchlorates and tetrafluoroborates. These potentials are limited in the cathodic direction by the reduction of the tetraalkylammonium cation (forming an amalgam at mercury[9]) in all the solvents examined except methylene dichloride, which is itself reduced at a potential of $-1.8$ V. The limiting anodic potential is determined by oxidation of the solvent, which occurs at 3.0 V for acetonitrile and 1.8 V for both DMF and $CH_2Cl_2$. We have used these tetraalkylammonium trifluoromethanesulfonates as supporting electrolytes for a variety of anodic and cathodic cyclic voltametric studies as well as for controlled potential bulk electrolyses, and find that they are comparable in every respect to their perchlorate or tetrafluoroborate counterparts, with the exceptions that the trifluoromethanesulfonate anion is nonoxidizing and does not react with highly oxidized substrates.

The obvious advantages of using the trifluoromethanesulfonates over the perchlorates necessitates their economical preparation, and, while the neutralization of the appropriate tetraalkylammonium hydroxide, or methathesis of the bromides, by trifluoromethanesulfonic acids presents a simple and efficient preparation, the use of a preformed tetraalkylammonium cation adds considerably to the expense of the final product. Esters of trifluoromethanesulfonic acid are

(4) H. Suschitzky, *Advan. Fluorine Chem.*, **4**, 1 (1965).

(5) R. H. Felton, personal communication. This sample of tetra-*n*-propylammonium perchlorate was prepared from the corresponding hydroxide and perchloric acid. The product was thoroughly washed with water and recrystallized from ethanol. The recrystallized sample (100 g) was placed in a plastic desiccator, attached directly to a vacuum pump, evacuated to $10^{-4}$ Torr, and left at room temperature. After some time, while still attached to the pump, the sample exploded and blew the top off the desiccator.

(6) T. Gramstad, *Tidsskr. Kjemi, Bergv. Met.*, **19**, 62 (1959).

(7) A. Streitwieser, Jr., C. L. Wilkins, and E. Kiehlmann, *J. Amer. Chem. Soc.*, **90**, 1598 (1968).

(8) A. Scott, and H. Taube, *Inorg. Chem.*, **10**, 62 (1971).

(9) J. D. Littlehailes and B. J. Woodhall, *Chem. Commun.*, 665 (1967).

TABLE II.—SPECIFIC RESISTANCES FOR TETRAALKYLAMMONIUM SALTS[b]

| | DMF | | $CH_3CN$ | | $CH_2Cl$ | | THF | |
|---|---|---|---|---|---|---|---|---|
| $Et_4N^+CF_3SO_3^-$ | 47.4 | (1.0) | 23.6 | (1.0) | 75.0 | (1.0) | | |
| | 63 | (0.5) | 32.7 | (0.5) | 145 | (0.5) | | |
| | 121 | (0.2) | 57.5 | (0.2) | 414 | (0.2) | | |
| | 205 | (0.1) | 96.6 | (0.1) | 9.6 | (0.1) | | |
| $Et_4N^+ClO_4^-$[a] | 52 | (0.6) | 26 | (0.6) | | | | |
| $Et_4N^+BF_4^-$[a] | 38 | (1.0) | 18 | (1.0) | | | | |
| | 54 | (0.5) | 27 | (0.5) | | | | |
| $Pr_4N^+CF_3SO_3^-$ | 67.6 | (1.0) | 32 | (1.0) | 89.3 | (1.0) | | |
| | 78 | (0.5) | 38 | (0.5) | 152 | (0.5) | | |
| | 137 | (0.2) | 64.3 | (0.2) | 388 | (0.2) | | |
| | 232 | (0.1) | 108 | (0.1) | 840 | (0.1) | | |
| $Pr_4N^+ClO_4^-$[a] | 64 | (0.6) | 31 | (0.60) | | | | |
| $Pr_4N^+BF_4^-$[a] | 51 | (1.0) | 23 | (1.0) | | | | |
| $Bu_4N^+CF_3SO_3^-$ | 93 | (1.0) | 43.4 | (1.0) | 139 | (1.0) | 322 | (1.0) |
| | 89 | (0.5) | 44.4 | (0.5) | 185 | (0.5) | 478 | (0.5) |
| | 146 | (0.2) | 77.2 | (0.2) | 409 | (0.2) | 1285 | (0.2) |
| | 246 | (0.1) | 121 | (0.1) | 841 | (0.1) | 3080 | (0.1) |
| $Bu_4N^+ClO_4^-$[a] | 77 | (0.6) | 37 | (0.6) | | | 369 | (1.0) |
| | 82 | (0.5) | 39 | (0.5) | | | 583 | (0.5) |
| $Bu_4N^+BF_4^-$[a] | 69 | (1.0) | 31 | (1.0) | | | 373 | (1.0) |
| | 72 | (0.5) | 33 | (0.5) | | | 587 | (0.5) |

[a] Reference 3. [b] In ohm cm (concentration, $M$).

TABLE III.—LIMITING ANODIC AND CATHODIC POTENTIALS FOR TETRAALKYLAMMONIUM SALTS[a]

| | DMF | | | $CH_3CN$ | | | $CH_2Cl_2$ | | | THF | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $Pt^+$ | $Pt^-$ | $Hg^-$ | $Pt^+$ | $Pt^-$ | $Hg^-$ | $Pt^+$ | $Pt^-$ | $Hg^-$ | $Pt^+$ | $Pt^-$ | $Hg^-$ |
| $Et_4N^+CF_3SO_3^-$ | 1.8 | −2.2 | −2.65 | 3.0 | −2.5 | −2.8 | 1.8 | −1.6 | −1.7 | | | |
| $Et_4N^+ClO_4^-$[b] | 1.6 | −2.1 | −3.0 | | | −2.8 | | | | | | |
| $Et_4N^+BF_4^-$[c] | | | −2.72 | | | −2.70 | | | | | | |
| $Pr_4N^+CF_3SO_3^-$ | 1.85 | −2.3 | −2.7 | 3.0 | −2.4 | −2.6 | 1.8 | −1.7 | −1.8 | | | |
| $Bu_4N^+CF_3SO_3^-$ | 1.8 | −2.3 | −2.8 | 3.0 | −2.1 | −2.7 | 1.8 | −1.8 | −1.9 | 1.6 | −2.2 | −3.2 |
| $Bu_4N^+ClO_4^-$ | 1.5[b] | −2.5[b] | −3.0[b] | | | −2.77[c] | 1.8[b] | −1.7[b] | −1.9[b] | | | −2.9[c] |
| $Bu_4N^+BF_4^-$[c] | | | −2.80 | | | −2.74 | | | | | | −2.75 |

[a] The potentials are measured against $Ag/AgCl^+$ except in *b* and *c* (where the reference electrode is SCE) SCE is +242 mV and $Ag/AgCl^+$ +197 mV *vs.* the hydrogen electrode. [b] C. K. Mann, "Electro-analytical Chemistry," A. J. Bard, Ed., Arnold, London, 1969, p 57. [c] Reference 3.

powerful alkylating agents,[10] which suggested that the treatment of such an ester with a tertiary amine should give directly the tetraalkylammonium salt. This proved to be the case, and our standard method for the preparation of these salts now follows this route.

## Experimental Section[11]

**Tetraethylammonium Trifluoromethanesulfonate.**—To 50 g (34 mmol) of a 10% solution of tetraethylammonium hydroxide in water was added 5 g (33 mmol) of trifluoromethylsulfonic acid. The solution was stirred for 30 min and then taken down to dryness on a rotary evaporator to give a quantitative yield of the crude salt, mp 140°. Three recrystallizations from THF gave 6.0 g (65%) of $Et_4NCF_3SO_3$: mp (after drying under vacuum) 160–161°; ir ($CH_2Cl_2$) no OH absorption, bands at 1250, 1228 (sh), 1162, and 1035 $cm^{-1}$; nmr ($CHCl_3$) $\delta$ 1.39 (12 H, t, $J$ = 7 Hz), 3.44 (8 H, q, $J$ = 7 Hz).

*Anal.* Calcd for $C_9H_{20}F_3NO_3S$: C, 38.70; H, 7.23; N, 5.01; S, 11.48. Found: C, 38.97; H, 7.40; N, 5.17; S, 12.01.

**Tetra-*n*-propylammonium Trifluoromethanesulfonate. Method A.**—A solution of 100 g (0.375 mol) of tetra-*n*-propylammonium bromide in 200 ml of water was rapidly stirred while 57.4 g (0.376 mol) of trifluoromethanesulfonic acid was slowly added. The solution was cooled to room temperature and filtered, and the product was washed with water. This gave 115 g (91%) of the crude salt, mp 149–163°. Recrystallization from methylene dichloride–benzene gave 101.2 g (80%) of $(n\text{-Pr})_4NCF_3SO_3$ as clear plates: mp (after drying under vacuum) 164.5–165.5°; ir ($CH_2Cl_2$) no OH absorption, bands at 1238, 1223, 1155, and 1031 $cm^{-1}$; nmr ($CH_2Cl_2$) $\delta$ 1.1 (12 H, t, $J$ = 7 Hz), 1.5–2.1 (8 H, m), and 3.1–3.35 (8 H, m).

*Anal.* Calcd for $C_{13}H_{28}F_3NO_3S$: C, 46.55; H, 8.41; N, 4.18; S, 9.50. Found: C, 46.75; H, 8.44; N, 4.22; S, 9.59.

**Method B. Trifluoromethanesulfonic Anhydride.**—A well-mixed suspension of 60 g (0.40 mol) of trifluoromethanesulfonic acid and 60 g (0.42 mol) of phosphorus pentoxide was allowed to stand at room temperature for 1 hr. The volatile product was then distilled, at 12 mm, into a Dry Ice–acetone trap, giving 46 g (87%) of the anhydride which was used without further purification.

A solution of 10 g (35.5 mmol) of trifluoromethanesulfonic anhydride and 45 ml of dry methylene dichloride was stirred and cooled in an ice bath. Dry pyridine (2.80 g, 35.5 mmol) was slowly added while the temperature was maintained below 10°, dry *n*-propanol (2.13 g, 35.5 mmol) was then slowly added, and the mixture was filtered. The filtrate, containing the propyl trifluoromethanesulfonate, was cooled in an ice bath and 5.1 g (35.6 mmol) of tri-*n*-propylamine (purified by distillation from naphthyl isocyanate) was slowly added. The solution was taken down to dryness. The residue was dissolved in the minimum of hot water and allowed to stand at 0° until crystallization was complete. The product, 8.9 g (75%), was collected by filtration; recrystallization gave a product identical with that described above.

**Tetra-*n*-butylammonium Trifluoromethanesulfonate. Method A.**—A solution of 9.7 g (30 mmol) of $(n\text{-Bu})_4NBr$ in 30 ml of water was rapidly stirred while 4.5 g (30 mmol) of trifluoromethanesulfonic acid was slowly added. After cooling to room temperature the mixture was filtered and the product was washed with water to give 8.82 g (75%) of the crude salt, mp 109–111°. The filtrate was extracted with methylene dichloride to give a further 2.68 g (23%) of the salt, mp 100–104°. The combined solids were twice recrystallized from methylene dichloride–ether to give 10.72 g (91%) of $(n\text{-Bu})_4NCF_3SO_3$: mp (after drying

(10) R. L. Hansen, *J. Org. Chem.*, **30**, 4322 (1965).

(11) Melting points are uncorrected. Nmr spectra were recorded at 60 MHz with tetramethylsilane as internal reference.

under vacuum) 111–112.5°; ir ($CH_2Cl_2$) no OH absorption, bands at 1235, 1220, 1154, and 1031 $cm^{-1}$; nmr ($CHCl_3$) δ 1.0–1.25 (12 H, m), 1.4–2.1 (16 H, m), and 3.15–3.65 (8 H, m).

*Anal.* Calcd for $C_{17}H_{36}F_3NO_3S$: C, 52.15; H, 9.27; N, 3.58; S, 8.19. Found: C, 52.17; H, 9.23; N, 3.65; S, 8.38.

**Method B.**—A solution of 10 g (35.5 mmol) of trifluoromethanesulfonic anhydride and 4.5 ml of methylene dichloride was stirred and cooled in an ice bath. Dry pyridine (2.80 g, 35.5 mmol) was slowly added while the temperature was maintained below 10°. Dry *n*-butyl alcohol (2.63 g, 35.5 mmol) was then slowly added and the mixture was filtered. The filtrate, containing the butyl trifluoromethanesulfonate, was cooled in an ice bath and 6.58 g (35.5 mmol) of tri-*n*-butylamine (purified by distillation from naphthyl isocyanate) was slowly added. The solution was taken down to dryness and the solid was triturated with ether. The ethereal solution was filtered and taken down to dryness, and the product was recrystallized as above to give 6.9 g (50%).

**Purification of Solvents.**—Methylene dichloride was refluxed for 24 hr over, and distilled from, calcium hydride under argon, and stored over 3A and 5A molecular sieves. The specific resistance was $1.44 \times 10^6$ ohm cm.

Acetonitrile was refluxed for 2 days over, and then distilled from, calcium hydride (10 g/l.) under argon. This distillate was then twice distilled from $P_2O_5$ (5 g/l.) under argon and stored over 3A molecular sieves. The specific resistance was $9.9 \times 10^5$ ohm cm.

Dimethylformamide (spectra grade, Eastman) was stored over 4A molecular sieves. The specific resistance was $5.67 \times 10^5$ ohm cm.

Tetrahydrofuran was refluxed over and distilled from sodium–potassium alloy under argon.

**Solubility Measurements.**—Mixtures of the purified solvents and an excess of the salt (pulverized and dried under vacuum at 50°) were heated until most of the salt had dissolved and then held at 28° until equilibrium was reached. Three separate aliquots of the supernatant liquid were then taken down to dryness and dried to constant weight under vacuum.

**Specific Resistance Measurements.**—Measurements were made using an Industrial Instruments conductivity cell with platinized platinum electrodes. The cell constant (0.098) was determined using 0.100 and 0.010 *M* aqueous solutions of KCl. Solutions were protected from the atmosphere and immersed in an oil bath maintained at 25.0°. The resistances were measured on a Serfass conductivity bridge, Model RCM 15, at a frequency of 1 KHz.

**Measurements of Limiting Anodic and Cathodic Potentials.**—A mercury drop (25.1 $mm^2$), hanging from the end of a capillary, was used for the cathodic measurements against mercury, and a platinum disc (7.1 $mm^2$) was used for the anodic and cathodic measurements against platinum. The reference electrode consisted of a long, thin (0.4 × 15 cm) tube with a cracked tip at the bottom. This tube was filled with the solvent and supporting electrolyte under investigation, and the aqueous reference electrode was isolated *via* a KCl–agar bridge placed in it. The counter electrode was in every case a small platinum sphere. Readings were taken using an M. I. Associates polarographic instrument with a Tetronics oscilloscope for the display. The limiting potential was taken to be that voltage at which $dI/dV$ equalled $5 \times 10^{-6}$ A $V^{-1}$.

**Registry No.**—$Et_4NCF_3SO_3$, 35895-69-3; $(n\text{-}Pr)_4NCF_3SO_3$, 35925-48-5; $(n\text{-}Bu)_4NCF_3SO_3$, 35895-70-6; $Et_4NBF_4$, 429-06-1.

## Synthesis of the Housefly Sex Attractant

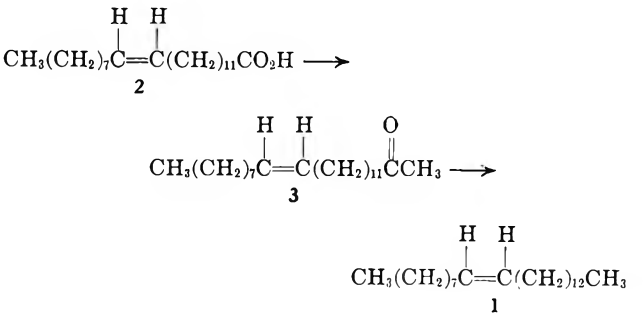
ROBERT L. CARGILL* AND M. G. ROSENBLUM

*Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208*

*Received June 6, 1972*

The isolation, identification, and one synthesis of the sex attractant, (*Z*)-9-tricosene (**1**), of the housefly (*Musca domestica* L.) were recently reported.[1] We described here a very efficient synthesis of **1** from readily available starting materials.

Erucic acid (**2**)[2] was converted into ketone **3** by the action of 2 equiv of methyllithium.[3] Huang-Minlon reduction[4] of **3** gave **1** in an overall yield of 85%. This




process is easily adaptable to large-scale preparations and requires no expensive reagents.

### Experimental Section[5]

**(*Z*)-Tricos-14-en-2-one (3).**—To a 10.7-g (31.3 mmol) quantity of erucic acid (**2**) (Columbia Organic Chemicals) in dry ether (200 ml) containing *o*-phenanthroline (5 mg) was added 31.5 ml (63.0 mmol) of 2.00 *M* methyllithium in hexane (Lithcoa), at a rate such that gas evolution was moderate. The reddish-brown reaction mixture was stirred for 30 min and quenched by cautiously adding 10% NaOH (100 ml), saturated $NaHCO_3$ (10 ml), and saturated $(NH_4)_2SO_4$ (10 ml). The phases were separated and the aqueous phase was extracted with ether (3 × 100 ml). The combined organic phases were dried ($MgSO_4$), concentrated, and distilled to give 9.77 g (93.3%) of ketone **3**: bp 140° (0.10 mm); $n^{23}D$ 1.4572; ir ($CCl_4$) 3015 (olefinic CH), 1725 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 0.88–2.50 (m, 42 H, all protons except olefinic; $CH_3$ s at δ 2.00), 5.27 [t, *J* (apparent) ≅ 4.5 Hz, 2 H, olefinic]; mass spectrum (70 eV) showed $M^{\cdot+}$ at *m/e* 336; vpc (3% SE-30, 8 ft × 0.125 in., 250°, 50 ml/min) showed one peak.

*Anal.* Calcd for $C_{23}H_{44}O$: C, 82.07; H, 13.18. Found: C, 82.04; H, 13.30.

**(*Z*)-9-Tricosene (1).**—To a solution of 3.1 g (47 mmol) of 85% KOH in diethylene glycol (30 ml) was added 4.77 g (14.1 mmol) of ketone **3** and 2.0 g (40 mmol) of 85% hydrazine hydrate. The reaction mixture was heated at 140° until the water had been removed and then at 193° for 4 hr. The cooled reaction mixture was poured into ice–water (150 ml), neutralized with 6 *N* HCl, and extracted with pentane (5 × 100 ml). The combined extracts were dried ($MgSO_4$), concentrated, and distilled to give 4.55 g (88.8%) of olefin **1**: bp 170–172° (0.5 mm); $n^{23}D$ 1.4532 [lit.[1] bp 157–158° (0.1 mm); $n^{26}D$ 1.4517]; ir ($CCl_4$) 3015 $cm^{-1}$ (olefinic CH); nmr ($CCl_4$) δ 0.67–2.25 (m, 44 H, all protons except olefinic; $CH_2CH{=}CHCH_2$ m, at δ 1.98), 5.25 [t, *J* (apparent) ≅ 4.5 Hz, 2 H, vinyl]; mass spectrum (70 eV) showed $M^{\cdot+}$ at *m/e* 322; vpc (3% SE-30, 8 ft × 0.125 in., 250°, 50 ml/min) showed one peak.

*Anal.* Calcd for $C_{23}H_{46}$: C, 85.63; H, 14.37. Found: C, 85.75; H, 14.30.

**Registry No.**—**1**, 27519-02-4; **3**, 36706-99-7.

(1) D. A. Carlson, M. S. Mayer, D. L. Silhacek, J. D. James, M. Beroza, and B. A. Bierl, *Science*, **174**, 76 (1971).

(2) Erucic acid is available commercially, or it can be isolated from rapeseed oil: C. R. Noller and R. H. Talbot, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 258.

(3) M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).

(4) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(5) Microanalyses were performed by Alfred Bernhardt Microanalytisches Laboritorium, Elbach über Engleskirchen, Mülheim (Ruhr), West Germany.

# Communications

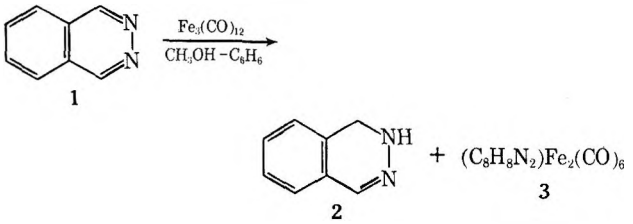
See Editorial, *J. Org. Chem.*, **37**, No. 24, 4A (1972)

## A Convenient Reduction of the Carbon–Nitrogen Double Bond

*Summary:* The carbon–nitrogen double bond can be conveniently reduced by reaction of the appropriate organic (or organometallic) compound with a mixture of triiron dodecacarbonyl [$Fe_3(CO)_{12}$] and methanol in benzene.

*Sir:* Recent interest in the use of hydridoiron carbonyl complexes as reagents for hydrogenating $\alpha,\beta$-unsaturated carbonyl compounds[1] and for preparing aromatic amines from nitro compounds[2] prompts the author to communicate a new, simple method for reducing a carbon–nitrogen double bond.

Treatment of phthalazine (**1**) with $Fe_3(CO)_{12}$ in refluxing methanol–benzene for 12–16 hr {conditions which generate the hydridoundecacarbonyltriferrate anion [$HFe_3(CO)_{11}^-$]}, followed by chromatography on Florisil, gave 1,2-dihydrophthalazine (**2**, mp 83.5–85.0°) in 54% yield and a small amount of complex **3**. Controlled potential electrolysis is the only other reported way for effecting direct conversion of **1** to **2**.[3]




1 2 3

The generality of this hydridoiron carbonyl reduction was demonstrated by similar reaction of $Fe_3(CO)_{12}$–$CH_3OH$ with a number of Schiff bases bearing various substituents. The results listed in Table I indicate

TABLE I

| Reactant | Product[a] | Yield, % |
|---|---|---|
| 1 | 2 | 54 |
| *N*-(*p*-Methoxybenzylidene)aniline | *p*-Methoxy-*N*-phenylbenzylamine | 52 |
| *p*-*n*-Butyl-*N*-(*p*-methoxybenzylidene)aniline | *p*-Methoxy-*N*-(*p*-*n*-butylphenyl)-benzylamine | 62 |
| *N*-Benzylideneaniline | *N*-Benzylaniline | 88 |
| *p*-Hexyloxy-*N*-(ferrocenylidene)-aniline | *p*-Hexyloxy-*N*-phenylferrocenyl-methylamine | 83 |
| *N*-(*p*-carbomethoxybenzylidene)aniline | *p*-Carbomethoxy-*N*-phenylbenzyl-amine | 71 |
| *N*-Isopropylidene-*n*-butylamine | Isopropyl-*n*-butylamine | 47 |

[a] Known products were identified by comparison of melting points and spectral data with those reported in the literature. Satisfactory analytical data was obtained for new compounds.

that this transformation occurs in reasonable–very good yields and hence shows promise as a synthetically useful organic reaction.

The following procedure is typical. A mixture of $Fe_3(CO)_{12}$ (2.67 g), dry methanol (2.7 ml), and dry benzene (35 ml) was refluxed with stirring under nitrogen for 2.25 hr. *p*-Hexyloxy-*N*-(ferrocenylidene)-aniline (1.56 g, 4.0 mmol), dissolved in benzene (10 ml), was added to the hydridoiron carbonyl solution and the resulting mixture was refluxed for 15 hr. The solution was cooled and filtered, and the filtrate was evaporated *in vacuo*. The residue from evaporation was chromatographed on Florisil to give *p*-hexyloxy-*N*-phenylferrocenylmethylamine on elution with petroleum ether (bp 38–50°).

**Acknowledgments** are made to the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Foundation of the State of New York, for support of this research. The author is indebted to Dr. L. Verbit for providing generous quantities of *p*-hexyloxy-*N*-(ferrocenylidene)aniline and *p*-*n*-butyl-*N*-(*p*-methoxybenzylidene)aniline.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF NEW YORK
AT BINGHAMTON
BINGHAMTON, NEW YORK 13901

HOWARD ALPER

RECEIVED SEPTEMBER 6, 1972

(1) R. Noyori, I. Umeda, and T. Ishigami, *J. Org. Chem.*, **37**, 1542 (1972).
(2) J. M. Landesberg, L. Katz, and C. Olsen, *ibid.*, **37**, 930 (1972).
(3) H. Lund and E. T. Jensen, *Acta Chem. Scand.*, **24**, 1867 (1970).

## Formylation of Aromatic Compounds with Hexamethylenetetramine and Trifluoroacetic Acid

*Summary:* A variety of aromatic compounds have been converted to aldehydes *via* a facile formylation process employing hexamethylenetetramine and trifluoroacetic acid.

*Sir:* In the Duff reaction,[1–3] hexamethylenetetramine is employed, usually with glyceroboric acid, to convert highly activated aromatic compounds to their formyl derivatives. The process is quite limited in scope, having been most widely used in the conversion of phenols to *o*-hydroxybenzaldehyde derivatives. The required conditions are rigorous, and the yields are generally low.

When the hexamethylenetetramine is used in conjunction with trifluoroacetic acid, a variety of aromatic compounds, including simple hydrocarbons, can be converted to imine products which are transformed to the aryl aldehydes on hydrolysis (eq 1). The required

$$ArH + C_6H_{12}N_4 \xrightarrow[2.\ H_2O]{1.\ CF_3COOH} ArCHO \qquad (1)$$

conditions are mild, and good yields of pure products can be easily isolated. A high order of para regioselectivity is exhibited.

Thus, a mixture of 12.2 g of 2,6-xylenol (100 mmol),

(1) J. C. Duff, *J. Chem. Soc.*, 547 (1941).
(2) C. F. H. Allen and G. W. Leubner, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 866.
(3) L. N. Ferguson, *Chem. Rev.*, **38**, 230 (1946).

14.0 g of hexamethylenetetramine (100 mmol), and 150 ml of trifluoroacetic acid was heated at reflux (83–90°) for 12 hr. The products were concentrated and combined with 600 ml of ice water; the resultant mixture was stirred for 15 min, made basic with $Na_2CO_3$, and extracted with ether. Evaporation of the ether solution left a yellow solid which was recrystallized from chloroform–pentane to afford 14.3 g (95% yield) of 3,5-dimethyl-4-hydroxybenzaldehyde, mp 111–112.5° (lit.[4] mp 113–114°).

The data for a number of these transformations are summarized in Table I.

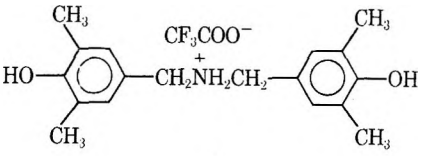
TABLE I
FORMYLATION OF AROMATICS BY HEXAMETHYLENETETRAMINE IN TRIFLUOROACETIC ACID

| Aromatic | Hexamethylenetetramine:aromatic | Product[a] (% yield) |
|---|---|---|
| *tert*-Butylbenzene | 1:1 | *p*-*tert*-Butylbenzaldehyde (75) |
| *p*-Xylene | 1:1 | 2,4-Dimethylbenzaldehyde (55) |
| Toluene | 1:1 | *p*-Tolualdehyde (50)<br>*o*-Tolualdehyde (11) |
| Benzene[b] | 1:4 | Benzaldehyde (32) |
| 2,6-Dimethylanisole | 2:1 | 3,5-Dimethyl-4-methoxybenzaldehyde (74) |
| Benzodioxane(1,4) | 1:1 | 4′-Formylbenzodioxane(1,4) (37), 3′-formylbenzodioxane(1,4) (2) |
| Diphenyl ether | 2:1 | *p*-Phenoxybenzaldehyde (29), 4,4′-diformyldiphenyl ether (25) |
| 2,6-Di-*tert*-butylphenol | 1:1 | 3,5-Di(*tert*-butyl)-4-hydroxybenzaldehyde (60) |
| 2,6-Xylenol | 1:1 | 3,5-Dimethyl-4-hydroxybenzaldehyde (95) |

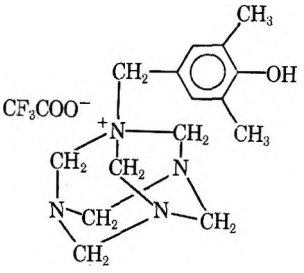
[a] Isolated materials exhibiting correct physical and spectroscopic properties; isomer compositions were by $^1H$ nmr spectroscopy. [b] Sealed tube, 125–150°.

Methylimine derivatives are immediate precursors of the aldehydes. When the reaction products derived from toluene were subjected to rapid hydrolytic work-up, the *p*- and *o*-toluimines $CH_3C_6H_4CH{=}NCH_3$ were obtained in predominance to the carbonyl compounds. Whether such products are formed by rearrangement of the methyleneimines $ArCH_2N{=}CH_2$ or arise in exchange reactions involving methylamine remains to be determined.

Other kinds of intermediates are isolable when both heating and hydrolysis are avoided. Thus, the 2,6-xylenol–hexamethylenetetramine–trifluoroacetic acid system when kept below 30° for 3 hr yielded a complex mixture from which the dibenzylammonium salt[5] **1** (41%) and the hexaminium salt[6] **2** (15%) were isolated



**1**



**2**

after evaporation of the acid and fractional crystallization of the residue from acetonitrile–ether. No unalkylated 2,6-xylenol was recovered.

The formation of **2** makes evident the relationship of this process to the Sommelet[7] and Delépine[8] reactions, both of which are based on transformation of *N*-benzyl derivatives of hexamethylenetetramine. Experiments with the trifluoroacetic acid system aimed at an illumination of these mechanistically obscure[9] facets of hexamethylenetetramine chemistry are in progress.

(4) V. V. Ershov and G. A. Zlobina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2235 (1964).

(5) Bis(4-hydroxy-3,5-dimethylbenzyl)ammonium trifluoroacetate (**1**): mp 193–195°; $^1H$ nmr (DMSO-$d_6$) δ 2.30 (s, 12), 4.08 (s, 4), 7.26 (s, 4), 9.18 (br, 2), 9.80 (br, 2); Fourier transform $^{13}C$ nmr (DMSO-$d_6$, from TMS) 153.2, 129.4, 123.8, 121.3, 48.9, 15.7 ppm. *Anal.* Calcd for $C_{20}H_{24}F_3O_4N$: C, 60.14; H, 6.06; F, 14.24; N, 3.51. Found: C, 60.26; H, 6.14; F, 14.36; N, 3.51.

(6) 4-Hydroxy-3,5-dimethylbenzylhexamethylenetetrammonium trifluoroacetate, (**2**): mp 154° dec; $^1H$ nmr (DMSO-$d_6$) δ 2.27 (s, 6), 3.55 (br, 2) 4.05 (s, 2), 4.67 (s, 6), 5.20 (s, 6), 7.25 (s, 2), 9.20 (br, 1); Fourier transform $^{13}C$ nmr (DMSO-$d_6$, from TMS) 155.4, 132.4, 125.1, 115.6, 77.7, 70.2, 59.6, 16.7 ppm. *Anal.* Calcd for $C_{16}H_{23}N_4O_3F_3$: C, 51.06; H, 6.16; N, 14.89; F, 15.14. Found: C, 51.27; H, 6.03; N, 14.80; F, 15.30.

(7) S. J. Angyal, *Org. React.*, **8**, 197 (1954).

(8) M. Delépine, *Bull. Soc. Chim. Fr.*, **13**, 358 (1895).

(9) Methyleneimmonium[10] and methylenebenzylimmonium[11] ions have been invoked as the oxidizing agents in the Sommelet reaction, in which aldehydes are produced on hydrolysis of hexaminium salts. Both species are likely alkylating agents in the process reported here. The seemingly high sensitivity to steric effects of substituents on the aromatic nucleus does suggest, however, that the alkylation involves bulkier electrophile(s), possibly ones more immediately derived from hexamethylenetetramine.

(10) H. R. Snyder and J. R. Demuth, *J. Amer. Chem. Soc.*, **78**, 1981 (1956).

(11) S. J. Angyal, *et al.*, *J. Chem. Soc.*, 1742 (1953).

CHEMICAL LABORATORY
GENERAL ELECTRIC RESEARCH
AND DEVELOPMENT CENTER
SCHENECTADY, NEW YORK 12301

WILLIAM E. SMITH

RECEIVED SEPTEMBER 20, 1972

## Facile Thermal Rearrangements of Allyl Selenides and Diselenides. [1,3] and [2,3] Shifts

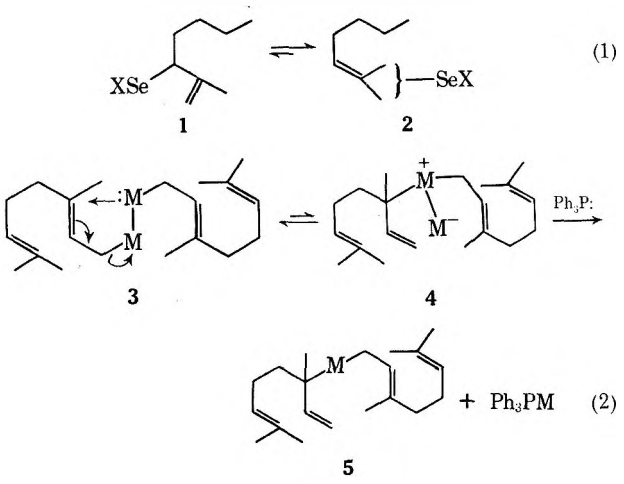
*Summary:* Allyl selenides and allyl diselenides undergo [1,3] and [2,3] shifts, respectively.

*Sir:* We wish to report the selenoallylic rearrangement[1,2] of **1** to **2** and the [2,3] sigmatropic rearrangement–reduction[3] of **3** (M = Se) to **5** (M = Se) (eq 1 and 2). The secondary allyl selenide **1** (X = Ph)

(1) The analogous thioallylic rearrangement has been studied by H. Kwart and N. Johnson, *J. Amer. Chem. Soc.*, **92**, 6064 (1970).

(2) A related [1,3] silallylic rearrangement has also been described by H. Kwart and J. Slutsky, *ibid.*, **94**, 2515 (1972).

(3) The analogous rearrangement–reduction of allylic disulfides has been studied by G. Höfle and J. E. Baldwin, *ibid.*, **93**, 6307 (1971); the synthesis of geranyl linalyl sulfide (**5**, M = S), *via* this sequence, the exact analog of reaction 2, was reported by G. M. Blackburn and W. D. Ollis, *Chem. Commun.*, 1261 (1968).




(1)

(2)

was prepared by addition of the corresponding allyl chloride (obtained by the action of Lee's reagent[4] on 2-methyl-1-hepten-3-ol) to a solution of PhSeNa in ethanol.[5] Selenide **1** (X = Ph) contained, by nmr analysis, about 6% *Z*–*E* isomers of **2** (X = Ph). Attempted short-path distillation of selenide **1** resulted in quantitative rearrangement of **1** to **2**, proceeding with a half-life of ~1.3 hr in chloroform at 52°. At the same temperature in methanol the rearrangement went at a somewhat slower rate ($t_{1/2}$ 2.0 hr). Thus, the selenoallylic rearrangement occurs more readily[6] than its thioallylic[1] partner.

All attempts to prepare the selenocyanate (X = CN) and diselenide (X = $SeC_7H_{15}$) analogs of **1** led only to the rearranged isomers (**2**) with selenium bound to the primary carbon. The [1,3] shift must occur very readily for selenocyanate **1** (X = CN). The failure to isolate the diselenide **1** (X = $SeC_7H_{15}$) could also be attributed to fast [1,3] shifts, but it is more likely due to double [2,3] sigmatropic rearrangement analogous to the situation for diallyl disulfides.[3] Reaction of geranyl chloride (prepared from geraniol using the Lee reagent[4]) with potassium selenocyanate in acetone[7] produced geranyl selenocyanate (**6**) in quantitative yield. Reduction of selenocyanate **6** with lithium aluminum hydride in ether gave geranylselenol and no geranyl amine.

Alkylation of $Na_2Se_2$, prepared in liquid ammonia by sodium metal reduction of metallic selenium,[8] with geranyl chloride resulted in a 2:1 mixture of geranyl diselenide **1** (M = Se) and geranyl monoselenide (**7**). The colorless monoselenide **7** was separated from the yellow diselenide by column chromatography on silica gel eluting with hexane. When geranyl diselenide **3** (M = Se) was exposed to excess triphenylphosphine in chloroform solution at 25°, geranyl linalyl selenide[9] (**5**, M = Se) was cleanly produced; the half-life for this process was ~2.5 hr. Thus, as for the [1,3] shift (reaction 1), the [2,3] shift (reaction 2) also proceeds faster[6] for the selenium analogs.

**Acknowledgment.**—We gratefully acknowledge the National Science Foundation (GP-30485X), Eli Lilly and Co., and Hoffmann-La Roche for support of this research.

(4) T. J. Nolan and J. B. Lee, *Can. J. Chem.*, **44**, 1331 (1966).

(5) The general procedure of Cope and coworkers was used except that thiophenol was replaced by selenophenol [A. C. Cope, D. E. Morrison, and L. Field, *J. Amer. Chem. Soc.*, **72**, 59 (1950)].

(6) Admittedly, the exact comparisons have not been made, but the rate data in ref 1 and 3 for the sulfur systems clearly support our contention that the selenium systems are more reactive.

(7) T. Tarantelli and D. Leonesi, *Ann. Chim. (Rome)*, **53**, 1113 (1963).

(8) L. Brandsma and H. E. Wijers, *Recl. Trav. Chim. Pays-Bas*, **82**, 68 (1963).

(9) All the organoselenium derivatives described in this report are new compounds and have been adequately characterized by analytical and spectral data. Some novel rearrangements occurring upon oxidation of these allyl selenium species are reported elsewhere: K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **94**, 7154 (1972).

DEPARTMENT OF CHEMISTRY K. B. SHARPLESS*
MASSACHUSETTS INSTITUTE OF TECHNOLOGY R. F. LAUER
CAMBRIDGE, MASSACHUSETTS 02139

RECEIVED SEPTEMBER 12, 1972

# Reprints from Chemical & Engineering News

**On orders of $10 or less please remit check or money order**

*Keeping broadly informed challenges every person today. If you missed these features from recent issues of C&EN, you can still get copies by filling in the coupon below.*

### Carbene Chemistry

*Dr. Robert A. Moss*
*Rutgers State University*
*New Brunswick, N.J.*
*June 16, 1969 & June 30, 1969* **75¢**

Carbenes are important in the synthesis of cyclopropanes and far more highly strained small ring compounds and, in fact, there's hardly a substrate, from steroids to elemental nitrogen, that hasn't been "hit" with a carbene. **06169**

### Chemical Origin of Cells

*Sidney W. Fox and Dr. Kaoru Harada, University of Miami; Dr. Gottfried Krampitz, University of Bonn; and Dr. George Mueller, University of Concepcion, Chile*
*June 22, 1970* **50¢**

We now have chemical and geological reasons to believe molecules evolved to primitive lifelike systems through rugged reactions, simply, quickly, often, and in many terrestrial locations. The answers so far available are simpler than those generally anticipated. The research has shown that the problem can be approached through chemical discipline; it need no longer be regarded as imponderable. **62270**

### Chemical Origins of Cells—2

*Sidney W. Fox*
*Institute of Molecular Evolution*
*Dec. 6, 1971, 8 pp.* **50¢**

In a sequel to his earlier feature article, Dr. Fox delves further into the origins of primitive replicating cells. **12671**

### Molecular Orbital Symmetry Rules

*Ralph G. Pearson*
*Northwestern University*
*Evanston, Ill.*
*September 28, 1970* **50¢**

Reaction mechanisms in both organic and inorganic chemistry have been so extensively and successfully studied in past years that in the 1960's it seemed impossible that any revolutionary advance could occur in this field. Yet chemists' recent realization of the importance of orbital symmetry effects in chemical reactions must be considered in the major breakthrough category. **92870**

### Ethylene

*Bruce F. Greek, C&EN*
*February 22, 1971* **50¢**

Another price-capacity-construction cycle under way. The ethylene cost-supply situation will interest management, engineering, and technical staff people alike. Taking the U.S. ethylene industry as a whole, future supply seems to rank above other concerns now as company research men and other planners revise their views for the next five years. **22271**

### Chemical Mutagens

*Howard J. Sanders, C&EN*
*May 19, 1969 & June 2, 1969* **75¢**

Geneticists, physicians, chemists, and growing segments of the public at large are becoming intensely aware of the possibility that drugs of all sorts, as well as pesticides, food ingredients and additives, industrial chemicals, and other substances, may be causing genetic damage in human general-body cells (somatic cells) and in germinal (sex cells). **05199**

### Heterocycles

*Alan R. Katritzky*
*University of East Anglia*
*England*
*April 13, 1970* **50¢**

The article examines some of the recent advances in heterocyclic chemistry—a field important to understanding biochemical mechanisms, natural-product chemistry, dyes, pharmaceuticals, and polymers. **41370**

### Electroorganic Synthesis

*Lennart E. Eberson*
*University of Lund, Sweden*
*Norman L. Weinberg*
*Hooker Chemical*
*Niagara Falls, N.Y.* **50¢**
*January 25, 1971*

A useful tool for synthetic organic chemists. Industry in general is making a very close reappraisal of electrochemical processing. Perhaps it is overly optimistic to expect electrolytic processes for the production of the most common organic chemicals, but such methods should certainly be of great interest to manufacturers of fine chemicals. **12571**

### Rubber

*Earl V. Anderson, C&EN*
*July 14, 1969* **50¢**

Today's rubber company reaches out in many directions. The traditional rubber products are still vital, to be sure. But rubber company interests now extend back to petrochemical raw materials for their elastomers and spill over into other chemicals, textiles, metals, aerospace, nuclear energy and, most important of all, into plastics. **71469**

### Fiber-Reinforced Plastics

*Michael Heylin, C&EN*
*February 1, 1971* **50¢**

Fiber-reinforced plastics ready for booming growth in the 70's. They have established footholds in several major markets, and they continue to attract the attention and the research funds of some of the biggest companies in the country. **02171**

### Food: Proteins for humans

*Aaron M. Altschul*
*U. S. Department of Agriculture*
*Washington, D.C.*
*Nov. 24, 1969* **50¢**

Worldwide, the overriding problem is poverty, thus economic problems must be solved in addition to improving natural foodstuffs and developing new ones. **11249**

### Free Radical Pathology

*William A. Pryor*
*Louisiana State University*
*Baton Rouge*
*June 7, 1971* **50¢**

Efforts have intensified in recent years to understand the mechanisms of aging at a molecular level and, as part of the program, a great deal of research has been done on the free radical theory of aging and the role of radical inhibitors such as vitamin E in the cell. **06771**

### Reinforced Plastics

*Gilbert R. Parker, C&EN*
*January 26, 1970* **50¢**

In the 1970-75 period reinforced plastics will enjoy many successes—in terms of sales, production, and earnings growth, product value, and acceptance. The industry, the products, and the consumers are examined in this article. **12670**

---

☐ 06169 ☐ 62270 ☐ 12670 ☐ 92870

☐ 22271 ☐ 05199 ☐ 41370 ☐ 12571

☐ 71469 ☐ 02171 ☐ 11249 ☐ 06771 ☐ 12671

TO: REPRINT DEPARTMENT

ACS Publications
1155 Sixteenth St., N.W.
Washington, D.C. 20036

FROM:

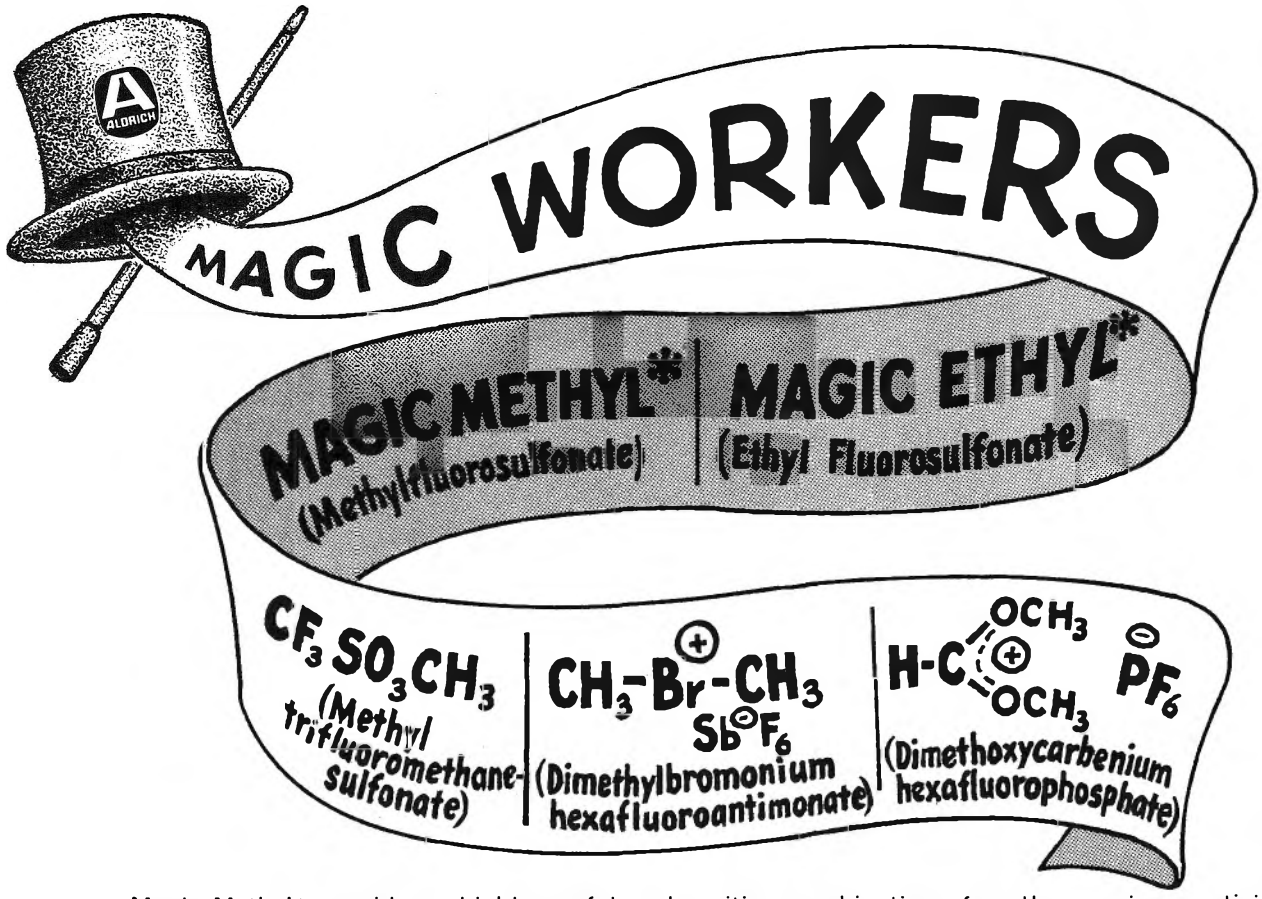
Name _____

Street _____

City _____

State _____ Zip Code

Amount enclosed $ _____




Magic Methyl* provides a highly useful and exciting combination of vastly superior reactivity and excellent stability. For example most ethers and carbonyl compounds form oxonium salts[1,2] with Magic Methyl*. In addition, amines, amides and carbamates are readily alkylated[1,3] and nitriles, sulfoxides and sulfides yield nitrilium, sulfoxonium and sulfonium salts.[1] The reduction of nitrilium salts with $NaBH_4$ yields secondary amines in a manner similar to that reported by Borch[4] for N-ethylnitrilium fluoroborates. Stevens rearrangement of sulfonium salts enables C-C bond formation.[5]

Magic Ethyl* and methyl trifluoromethanesulfonate also possess the high reactivity and stability associated with Magic Methyl.* Magic Ethyl* has obvious applications for ethylation in place of methylation while methyl trifluoromethanesulfonate has the advantage that it cannot react as a sulfonyl halide.[2]

Dimethylbromonium ion and dimethoxycarbenium ion, as their stable crystalline hexafluoroantimonate and hexafluorophosphate salts respectively, are useful as mild methylating reagents. The former is one[6] of Olah's newly discovered dialkylhalonium ions.

*References:*

1. M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnot and M. C. Whiting, Chem. Comm., 1533 (1968).
2. R. W. Alder, private communication.
3. M. G. Ahmed and R. W. Alder, Chem. Comm., 1389 (1969).
4. R. F. Borch, Chem. Comm., 442 (1968).
5. R. M. Mitchell and V. Boekelheide, Tetrahedron Lett., 1197 (1970).
6. G. A. Olah and M. B. Comisarow, J. Amer. Chem. Soc., **91**, 2955 (1969).

| | | | |
|---|---|---|---|
| 16,048-2 | Magic Methyl* (methyl fluorosulfonate) | 11.4g $ 3.00; | 100g $14.00 |
| 16,451-8 | Magic Methyl-$d_3$ (methyl-$d_3$ fluorosulfonate) | 1.2g $15.00; | 5g $60.00 |
| 17,759-8 | Magic Ethyl* (ethyl fluorosulfonate) | | 128g $20.00 |
| 16,428-3 | Methyl trifluoromethanesulfonate | 10g $ 8.50; | 50g $25.00 |
| 17,757-1 | Dimethylbromonium hexafluoroantimonate | | 25g $35.00 |
| 17,756-3 | Dimethoxycarbenium hexafluorophosphate | | 25g $25.00 |

**Trademark of Aldrich Chemical Co.*

*Write for new Aldrich HANDBOOK OF ORGANIC CHEMICALS listing over 18,000 chemicals*

**Aldrich Chemical Company, Inc.**

CRAFTSMEN IN CHEMISTRY

940 WEST SAINT PAUL AVENUE · MILWAUKEE, WISCONSIN 53233

In Great Britain: **RALPH N. EMANUEL Ltd.**
**264 Water Rd., Wembley, Middx., HAO 1PY, England**
In Continental Europe: **ALDRICH-EUROPE, B-2340 Beerse, Belgium**
In West Germany: **EGA-CHEMIE KG, 7924 Steinheim am Albuch**