THE PYRIMIDINES

Supplement II

D. J. Brown

THE AUSTRALIAN NATIONAL UNIVERSITY
CANBERRA

With a Chapter by

R. F. Evans

THE UNIVERSITY OF QUEENSLAND
BRISBANE

And Essays by

W. B. Cowden

and

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SUPPLEMENT II

This is the sixteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Consulting Editors

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To

My Research Students
Past and Present

who taught me far more about pyrimidine chemistry than I ever taught them:

BRIAN ENGLAND
PHIL FORD
ROY FOSTER
JOHN HOSKINS
KAZU IENAGA
NOEL JACOBSEN
TZOONG LEE
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TOM TEITEI
KAZUO SHINOZUKA
TAKASHI SUGIMOTO
PAUL WARING

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry "as readily accessible as possible", new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

The original volume, entitled *The Pyrimidines,* covered the literature published through 1957 and, subsequently, *The Pyrimidines, Supplement I* updated this coverage to 1967. The present volume, *The Pyrimidines, Supplement II,* continues this review process for the period 1968–1983, inclusive.

It is important to realize that *Supplement II* does not contain any information already recorded in the original volume or in *Supplement I.* Thus all three volumes must be used together in order to cover all the literature on any aspect of pyrimidine chemistry. Unfortunately, the two earlier volumes are now out of print but both can be obtained (at least for the present) as reprints from the Krieger Publishing Co., Inc., P.O. Box 9542, Melbourne, Florida, U.S.A., 32901.

To facilitate combined use of the three volumes, all section headings and tables in *Supplement II* include back references to the page numbers for corresponding sections or tables (if any) in the previous volumes; in such back references (as in *Beilstein*), page numbers of the original volume are preceded by *H* (for *Hauptwerk*) and those of *Supplement I* by *E* (for *Ergänzungswerk*).

Because of numerous complaints from users that the classified appendix tables of simple pyrimidines in the original volume and *Supplement I* were difficult to use effectively, such tables have been replaced in *Supplement II* by a single rather massive alphabetical table of simple pyrimidines described from 1968 to 1983. Although old fashioned in minor respects, the original nomenclature conventions (*H* 3) have been retained to assist in the combined use of all three volumes: In particular, it should be noted that all substituents are rendered as prefixes, the common tautomeric groups are rendered in their hydroxy or mercapto form, and "hydro" is considered as an alphabetically placed substituent. The original definition of a "simple pyrimidine" (*H* 501) has also been retained to regulate inclusion in the appendix table of pyrimidines; as before, references in that table are preceded by the letter(s) *H* and/or *E* when earlier information has also appeared in appropriate tables of the original volume and/or *Supplement I,* respectively. Except in a very few cases (indicated by inclusion of a *Chemical Abstracts* citation in the reference), all information in both text and tables has been gleaned from original publications, as flagged periodically in *Chemischer Informationsdienst*

and/or *Chemical Abstracts.* For obvious pragmatic reasons, patents have been ignored in general. As in *Supplement I,* references are given in a single list for simplicity. References prior to 4329 will be found in one or the other of the earlier volumes. The indexing conventions are similar to those outlined previously (*H* 677) and are summarized again immediately prior to the Index of this volume.

The origins of papers on pyrimidine chemistry are given below for the period 1968–1983. When compared with the figures for the previous decade, 1958–1967 (*E* ix), it is evident that the marked decrease in papers from the United States, the British Commonwealth, and to a lesser extent Germany, has been balanced by a phenomenal increase in papers from Japan and Russia, while other regional contributions have remained more or less static. Indeed, Japan now stands a very close second to the United States, and Russia is only just behind Germany.

United States of America	20.17%
Japan	18.60%
British Commonwealth (and India)	14.44%
Germany (East and West)	11.72%
Russia	11.21%
Eastern Europe	7.59%
France and Switzerland	5.78%
Netherlands and Belgium	3.72%
Austria	1.86%
Italy, Spain, and South America	1.76%
Scandinavia	1.32%
Others (Israel, China, Korea, etc.)	1.86%.

Many friends have assisted enormously in the preparation of this supplementary volume. Foremost are Drs. Bill Cowden, Russell Evans (kindly assisted by Mr. H. K. Edwards), and David Fenn, who completed appropriate sections on pyrimidine *N*-oxides, reduced pyrimidines, and the nmr spectra of pyrimidines, respectively. My colleagues, Drs. Wilf Armarego, Gordon Barlin, Doug Perrin, and Ernest Spinner never failed to proffer excellent advice. Kenya Mori assisted frequently in the translation of Japanese papers. Kerry McAndrew, Abira Hassan, and Barbara Cronin gave invaluable assistance in the library, in checking the typescript, and in other ways. Despite ill health, Janice White cheerfully prepared the greater part of the typescript from my appalling handwriting, a task to which

Diane Dick, Rosemary Enge, and Caroline Cobban also contributed as time permitted. To the above good people and to my wife for her patience during the years of weekend writing, I offer my sincere thanks.

D. J. BROWN

The Australian National University
Canberra, Australia
April 1985

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Tables Integrated with the Text

CHAPTER I

Introduction to the Pyrimidines (*H* 1, *E* 1)

Some important and useful advances made in pyrimidine chemistry since 1970 are included in this chapter. Hence it is broadly supplementary only to the fourth section of the original Ch. I. Moreover, no attempt is made herein to cover new or improved primary syntheses, which are highlighted in Ch. II and III of this supplement. Several brief but general reviews of pyrimidine chemistry have appeared recently in English,[6326, 6330] Italian,[6182] and German.[6183]

4. General Summary of Pyrimidine Chemistry (*H* 9, *E* 2)

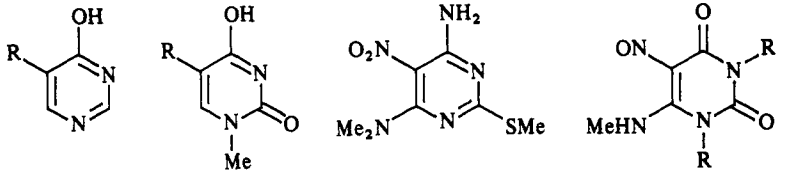
A. Electrophilic Substitution (*H* 10, *E* 2)

(1) *Nitration and Nitrosation* (*H* 10, *E* 2)

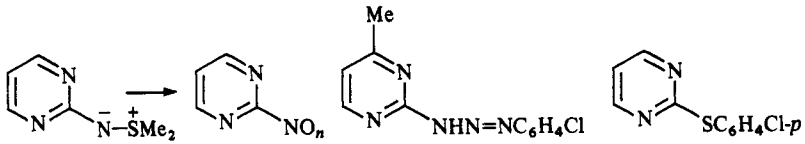
(Ch. V, Sects. 1 and 2)

The successful nitration of 2-hydroxypyrimidine by potassium nitrate in sulfuric acid at 100°, previously reported (*E* 96) from preliminary communications, has now been confirmed and extended to 4-hydroxypyrimidine (1, R = H),[5411] from which 4-hydroxy-5-nitropyrimidine (1, R = Me; 40% yield) was so made. In less difficult cases, a novel and effective procedure has been reported; the action of nitronium tetrafluoroborate in sulfolane at 20° converted 1-methyluracil (2, R = H) into its 5-nitro derivative (2, R = NO_2) in excellent yield, and analogues were made similarly.[5516] More and more examples of nitration in the presence of labile groups have emerged, as exemplified in the direct formation of 4-amino-6-dimethylamino-2-methylthio-5-nitropyrimidine (3) by using potassium nitrate/sulfuric acid at 0° (42%),[4617] or of 4-chloro-2,6-dimethoxy-5-nitropyrimidine (76%) by using fuming nitric

acid/sulfuric acid, initially at 5° and then at 80°.[5994] Work has continued on the nitration of phenylpyrimidines in the benzene ring,[5441, 5662, 5663, 6155] but it is still impossible to forecast the position(s) of nitration.



(1) (2) (3) (4)



(5) (6) (7) (8)

The poor yields obtained by regular nitrosation in aqueous media to afford 1,3-dialkyl-1,2,3,4-tetrahydro-6-methylamino-5-nitroso-2,4-dioxopyrimidines (4) have been improved dramatically by using isoamyl nitrite/ethanol; in this way, the 1,3-dicyclohexyl homologue (4, R = C_6H_{11}) was obtained in 42% yield. The oxidation of nitroso- to nitropyrimidines has continued to prove valuable. Indeed, the conversion of 2-amino- into 2-*S*,*S*-sulfimidopyrimidine (5) followed by oxidation to 2-nitrosopyrimidine (6, $n = 1$) and further oxidation by ozone to 2-nitropyrimidine (6, $n = 2$) has represented a landmark in pyrimidine chemistry, being the first 2/4-nitropyrimidine ever made.[6267]

(2) *Diazo Coupling* (*H* 11)

(Ch. V, Sect. 3.A)

Besides innumerable examples of diazo coupling at the 5-position and a few at the 4-position or on an activated methyl substituent, it has been pointed out that diazonium salts can attack amino or mercapto groups if the normal sites are insufficiently activated. This is seen in the formation of 2-*p*-chlorophenyldiazoamino-4-methylpyrimidine (7) or 2-*p*-chlorophenylthiopyrimidine (8).[6090]