ACRIDINES

Edited by

R. M. Acheson

The Department of Biochemistry
and
The Queen's College
University of Oxford

SECOND EDITION

INTERSCIENCE PUBLISHERS
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JOHN WILEY & SONS
NEW YORK • LONDON • SYDNEY • TORONTO

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This is the second edition of the ninth volume published in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

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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.

ARNOLD WEISSBERGER

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Preface

In the 15 years since the publication of the first edition, there have been many developments in acridine chemistry and biochemistry. These have taken place over a broad front, too broad in fact for one person to review the field both adequately and rapidly enough to ensure up-to-date publication. I have been very fortunate in having a number of colleagues who were willing and able to find the time necessary to revise the chapters of the first edition, or to write entirely new chapters where necessary, for this new edition. Building a book of contributed chapters always presents difficulties of possible duplication and accidental omission of material that is on the borderlines of two or more chapters. A small amount of overlap has resulted, but this has been left in order to maintain continuity in the individual chapters.

All those working with acridines should be grateful that agreement has now been achieved concerning the numbering of the acridine ring. The agreed system is that employed in both editions of this book, and by *Chemical Abstracts*, and the *Ring Index*, and recommended by the International Union of Pure and Applied Chemistry.

I should like to thank most sincerely all my co-authors, all of whom have given up much leisure time in order to help. I also wish to thank The Queen's College and The University of Oxford for leave during which the manuscript was edited, and Professor C. A. Grob for the hospitality of the Institute for Organic Chemistry, The University of Basel, which was greatly appreciated.

I also thank Miss M. B. Acheson, Mrs. R. F. Flowerday, Messers P. J. Abbott, M. P. Acheson, and N. D. Wright for their help in preparing the index, and Miss P. Lloyd for typing the copy. Last, but not least, I must express my gratitude to all those working in Wiley-Interscience and associated with this volume for their advice and continuous assistance, which greatly facilitated my task.

R. M. ACHESON

March 1972
The Department of Biochemistry
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The Queen's College
University of Oxford
Oxford, England

Contents

ACRIDINES

Second Edition

Nomenclature and Numbering System

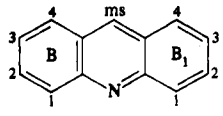
R. M. ACHESON

Department of Biochemistry, and The Queen's College, University of Oxford, England

The discovery of a new basic material in the anthracene fraction of coal tar was announced by Graebe and Caro[1] in 1870. On account of its acrid smell and irritating action on the skin and mucous membrane, this new substance was called "acridin" (acris = sharp, or pungent). Apart from the addition of a terminal "e," and the replacement of the "c" by "k" in a few older papers, this name has not subsequently been changed. The general nomenclature and numbering system employed for acridine and its derivatives in this monograph is the same as that used in *Chemical Abstracts* since 1937.

At least seven different systems of numbering have been used for the simple acridine ring system, and many more methods have been proposed for fused ring systems containing the acridine nucleus. Much difficulty, therefore, arises when a literature search for acridine derivatives becomes necessary, especially in regard to early publications.

The first numbering system (**1**) was suggested by Hess and Bernthsen[2] but found no support. Schöpff's system (**2**), suggested in 1892,[3] was almost as unpopular, although a slight modification (**3**) was used in 1922 and occasionally later.[4]



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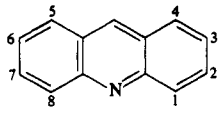

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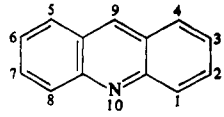
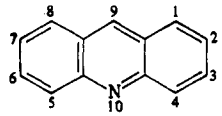


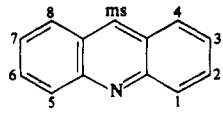
3

In 1893 Graebe,[5] the discoverer of acridine, suggested a numbering system (**4**) based on the then accepted numbering used for anthracene, xanthene, etc. This system was generally approved at the time. In 1900, however, method

(**5**), which was largely ignored, was propounded by von Richter in his textbook,[6] while in the same year M. M. Richter[7] used another system (**6**) in his *Lexikon der Kohlenstoff-Verbindungen.*



4
Graebe



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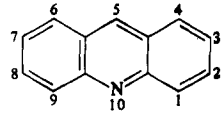
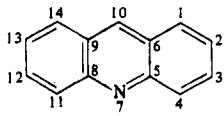


6
Richter

This method of numbering gained some popularity. Borsche[8] suggested another system (**7**), which did not find acceptance. In 1921 Stelzner[9] extended Graebe's system to **8**.



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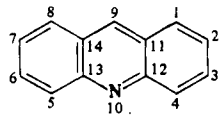
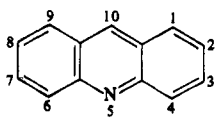


8

Another variation (**9**) suggested by Patterson,[10] which is in conformity with the *Ring Index* rules,[11] was used in a standard textbook[12] in 1926, but the numbering was changed to that of Graebe in the 1936 edition of the book. Yet another system[13] (**10**) appeared in 1947, adding to the confusion.



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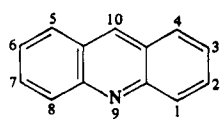


10

At the present time only two systems of numbering, **4** and **6**, are significantly used for acridine derivatives. A record was kept during the preparation of the first edition (1956) of this monograph of the number and year of publication of all original papers available and referred to (whether mentioned subsequently in the monograph or not) using these systems. Figure 1 shows the results. From the graph it is clear that (1) the great majority of publications use Graebe's system; and (2) although an increase in the popularity of Richter's system in recent years is evident, Graebe's system is still used in the majority of publications. The *Ring Index* has adopted the latter system, which is the same as that generally used for anthracene, although it is not consistent with Patterson's rules for the numbering of cyclic compounds.

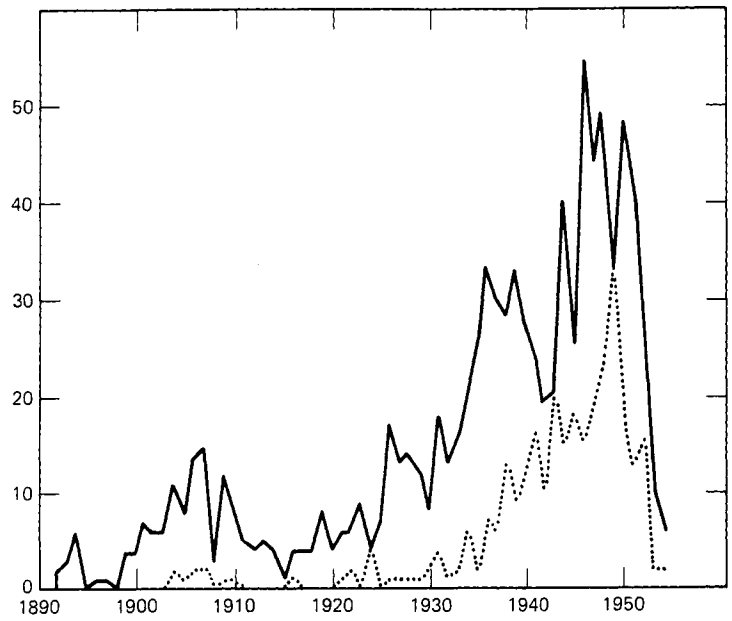


Fig. 1. The number of papers published yearly using Graebe's (———) and Richter's (. . . . .) systems.

Graebe's system of numbering is used in *Beilstein's Handbuch* and in *Chemisches Zentralblatt*. Until 1937 *Chemical Abstracts* officially used Richter's system of numbering; at that time a change was made to Graebe's system. *British Chemical Society Abstracts* uses Richter's system, which was also employed by Albert.[14] Although the British and American abstracts officially use particular methods of numbering, papers in which the numbering of acridine derivatives differs from that officially used in the abstracts may be abstracted in the original numberings. This calls for much care when using abstracts. The stage has even been reached at which both systems are used in the *same* chapter of a standard textbook.[15]

The continued use of two numbering systems for the acridine ring system added to the nomenclature difficulties, so that a decision as to which system should be used in the future became essential. This decision has recently been made (see below). The arguments put forward by Albert[14] in support of Richter's system (**6**) are:

(a) It has been used in a significant portion of the literature including almost the whole of the literature in the English language; (b) it makes no suggestion of there being more than five possible mono-derivatives whereas **4** gives rise to such names

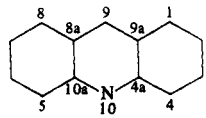
as 9-chloroacridine which suggests that there are nine; and (c) a number of medical products have been introduced in Britain and Australia in recent years not under trade names but described systematically according to **6**—e.g. 5-aminoacridine; it would be confusing to the physician if they should simultaneously be numbered in two ways, and he would be apt to think that two isomeric substances are involved.

The first statement is incorrect; the increase in popularity of Graebe's system is largely a result of its use in American publications. With regard to (b), it is necessary to point out that many accepted numbering systems involve this disadvantage, which is now unlikely to be a source of confusion. As to (c), the medical profession can be little interested in acridine nomenclature, since the systematic name "5-aminoacridine hydrochloride" (system **6**) has been officially replaced by "Aminacrine Hydrochloride B.P.," and the trade names for this substance, e.g., "Acramine," "Dermacrine," and "Monacrin," are widely used. Incidentally, in spite of his support for Richter's system, Albert has, in fact, found it convenient to use Graebe's system in one section (on carbazimes) in the first edition of his own monograph.[14]

From the evidence discussed above, it is clear that Graebe's system (**4**), which is employed throughout this monograph, is used in the large majority (ca. 75.3%) of the papers published before 1955 in which a numbering system is required, and in the more important abstract journals.

Richter's system (**6**) offers no particular advantage to compensate for its minority position and should therefore be completely dispensed with in the future. This view has also been taken by the Union of Pure and Applied Chemistry[16] and now appears to have been generally accepted.[17]

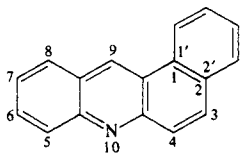
The carbon atoms common to both rings can bear substituents only when the acridine ring is suitably reduced, and in this situation it becomes necessary to number these positions. Albert[17] employs Stelzner's extension (**7**) of Graebe's system for these carbon atoms. This use is unfortunate and should be discontinued. It is inconsistent with the generally agreed rules for the numbering of such atoms, and it is inconsistent with current *Chemical Abstracts* practice. The atoms common to both rings should be numbered as shown in structure **11**.



11

Many arbitrary numberings, as well as generic numberings, have been used for fused ring systems containing the acridine nucleus. Generic numbering is built up from the numberings of the constituent ring systems regarded as being fused together, subscripts being used to differentiate between the figures. In this system **12** is 1′,2′-1,2-benzacridine, or 1,2-benzacridine, since this

simplification leads to no ambiguity. This type of numbering is much used in the German literature. A similar system, based on Richter's method of numbering acridine, is also largely used in *British Chemical Abstracts*. It was often used in *Chemical Abstracts* until 1937, when the *Ring Index* numbering was adopted for condensed acridines. In order to minimize the use of numbers and subscripts, the sides of the parent ring system have been lettered *a, b, c, . . .* (**13**) starting from position 1. Thus 1,2-benzacridine (**12**) becomes benz[*a*]-acridine, and **14** is 3′-methylbenz[*a*]acridine.



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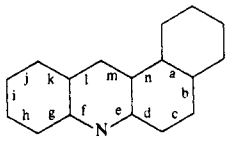

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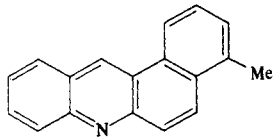


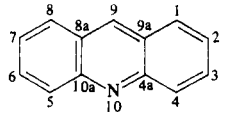
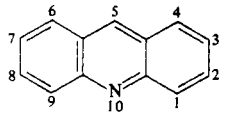
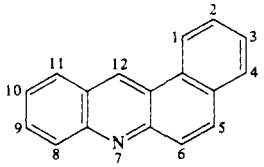
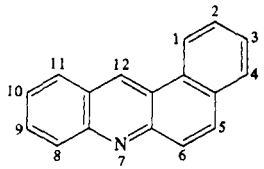
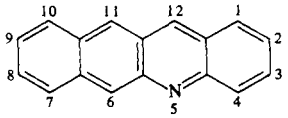
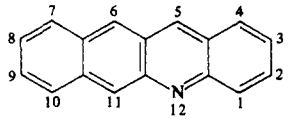
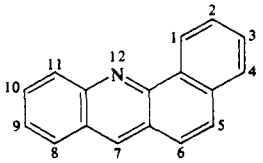
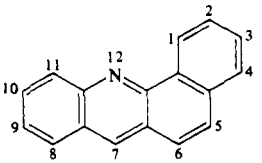
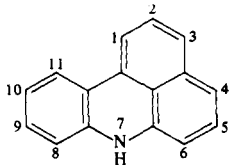
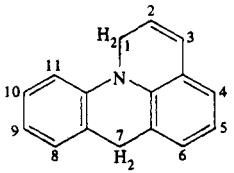
14

Although generic numbering for comparatively simple, fused ring systems has the advantage of being easily worked out from the numbering of the constituent ring systems, it has the disadvantage of requiring the use of many figures and brackets. For this reason, and in order to conform to current usage in *Chemical Abstracts*, the arbitrary *Ring Index*[10,18] numbering of condensed acridine derivatives has been adopted here. **14** is then known as 4-methyl-benz[*a*]acridine. The main disadvantage in using an arbitrary numbering system for polycyclic compounds is that similar compounds may have substantially different numberings. This, however, is a small price to pay for the convenience offered by a generally accepted, *and used*, numbering system. In view of the variety of current methods of numbering employed for condensed acridines, as much care is necessary when making a literature search for particular compounds of this type as in the case of simple acridine derivatives.

A variety of unsystematic and misleading names have been used in the past for most condensed acridines, an example being benz[*a*]acridine, which has also been referred to as β-chrysidine, β-phenonaphthacridine and 1,2-naphthacridine. Misleading nomenclature of the latter type is hardly ever used in current literature and should not be revived. The only remaining example of unsystematic nomenclature in the acridine series officially used by *Chemical Abstracts* until about 1957 is that of "carbazime" for 2,9-dihydro-2-iminoacridine. Obsolete names, as well as the *Chemical Abstracts* names and numberings used in this monograph for condensed acridines, are given in many cases when the individual compounds are discussed.

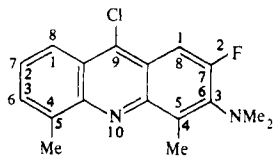
In the naming of a substituted acridine derivative, there are still two points to be considered. First, the lowest possible numbers should be chosen for the substituents; a full discussion of this is available in *Chemical Abstracts*[19]

TABLE I. Numbering Systems used for Acridine and the Benzacridines

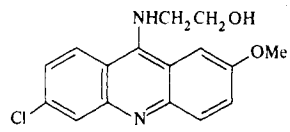
Compound and *Ring Index* number[18]	Numbering used here and in *Chem. Abstr.* from *1937*	Alternative (minority) used in *Chem. Abstr.* before *1937*
Acridine *R.R.I.* 3523 (*R.I.* 1973)[10]		
Benz[*a*]acridine *R.R.I.* 5144 (*R.I.* 2735)[10]		
Benz[*b*]acridine *R.R.I.* 5140 (*R.I.*2731)[10]		
Benz[*c*]acridine *R.R.I.* 5148 (*R.I.* 2737)[10]		
7(H)-Benz[*kl*]acridine *R.R.I.* 5564 (*R.I.* not listed)[10]		
1, 7(H)-Pyrid[3,2,1-*de*]acridine *R.R.I.* 5104 (*R.I.* 2712)[10]		

Note: The *Chemical Abstracts* numberings for more complicated condensed compounds are given in the sections in which the compounds are discussed.

and in International Union of Pure and Applied Chemistry publications.[20] Since the acridine ring can be numbered in either direction, **15** may be called either 9-chloro-6-dimethylamino-7-fluoro-4,5-dimethylacridine or 9-chloro-3-dimethylamino-2-fluoro-4,5-dimethylacridine, the latter being "correct." Such a compound, however, may be found "incorrectly" numbered in *Chemical Abstracts*. Second, substituents should be placed in alphabetical order, regardless of their number or position in the molecule, and compound radical names should be treated as a unit according to their first letter. Agreement on this issue has been reached between American and British workers.[21] For instance **15** should be called 9-chloro-3-*di*methylamino-2-*fl*uoro-4,5-di*m*ethylacridine, and not 9-chloro-4,5-dimethyl-3-dimethylamino-2-fluoroacridine. An order of preference for the last radical in the naming of complex organic compounds is also used by *Chemical Abstracts*: onium compound, acid, acid halide, amide, imide, amidine, aldehyde, nitrile, isocyanide, ketone, alcohol, thiol, amine, imine, ether, sulfide, sulfoxide, sulfone, etc. On this basis **16** should be known as 2-(6-chloro-2-methoxy-9-acridylamino)-ethanol.



15



16

However, the heterocyclic part of this molecule is generally considered more important than the aliphatic part, so that the compound is called 6-chloro-9-(2-hydroxyethylamino)-2-methoxyacridine in this monograph and usually in *Chemical Abstracts*, where it may also be indexed under its alternative name.

The system of numbering approved by the *Ring Index* and by the International Union of Pure and Applied Chemistry, used in this monograph and officially used in *Chemical Abstracts* for acridine and the benzacridines, and alternative numberings used in *Chemical Abstracts* before 1937, are given in Table I.

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CHAPTER I

Acridines

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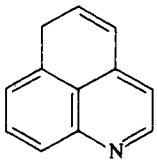
1. Historical Introduction and the Formulation of Acridine

It has been one hundred years since Graebe and Caro[1] announced the isolation of acridine in their report in the *Berichte*, "Wir geben derselben den Namen Acridin wegen der scharfen und beissenden Wirkung, die sie auf die Haut ausübt." The new basic material was isolated from the anthracene fraction of coal tar by extraction with dilute sulfuric acid, followed by precipitation as its dichromate. This compound, assigned the empirical formula, $C_{12}H_9N$, could be only incompletely characterized because of the small amount of material available. However, its appearance, melting point, steam volatility, stability, and ability to form a variety of well-crystallized salts were duly noted. From this stimulus have come a vast body of research and the varied useful applications of acridine and its derivatives known today.

Early experiments suggested the molecular formula $(C_{12}H_9N)_2$ for acridine.[2] Later its structure was considered[3] to be **1**, partly because alkaline permanganate oxidation gave acridinic acid,[4] a quinoline dicarboxylic acid, which on successive decarboxylation gave a quinoline monocarboxylic acid and quinoline. However, Riedel showed that this structure was not possible,[5] as the quinoline monocarboxylic acid obtained on degradation was identical with quinoline-3-carboxylic acid. He suggested that the earlier analyses were in error, that acridine had the molecular formula $C_{13}H_9N$ and was better represented by **2**. This was, in fact, proved correct by the



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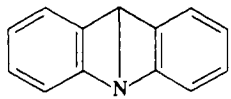

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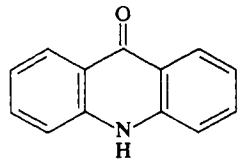

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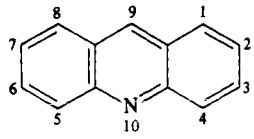
synthesis of acridine, although in poor yield, from *N*-formyldiphenylamine and zinc chloride;[6] 9-phenylacridine had been synthesized a few years before,[7] but its structure had not been recognized. The formation of 9-acridanone (**3**), both by the oxidation of acridine[3] and by the sulfuric acid cyclization of diphenylamine-2-carboxylic acid,[8] supported Riedel's view.

Following the early observation[9] that acridine reacted with sulfurous acid, methods for estimation[10] and extraction[11, 12] of acridine using aqueous sodium bisulfite have been devised. Acridine has been purified by its phosphate,[13] and can be estimated by titration in aqueous ethanol with sulfuric acid using phenolphthalein as the indicator,[14] or gravimetrically as the picrate[15] or perchlorate.[16] Spectrophotofluorimetric methods have recently been used for the detection and estimation of acridine in the airborne particulates of urban atmospheres.[17]

The methods used for the synthesis of acridines will be discussed in the next section.

The numbering system used for acridine in *Chemical Abstracts*, as shown in **4**, will be used throughout this discussion.



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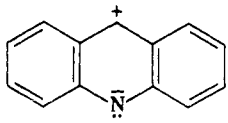
The structure of acridine is best represented, not with a centric bond, **2**, but in terms of an ordinary Kekulé structure, **4**, as first suggested by Hinsberg.[18] A more complete picture is derived from consideration of a resonance hybrid to which all possible Kekulé structures contribute, as well as the centric and the others shown here.[19] There may also be a minor contribution from **8**, where the electrons are unpaired and ready to participate in homolytic reactions. Such a representation is in accord with the optical exaltation,[20, 21] the highly conjugated ultraviolet (uv) absorption spectrum (which is considered in Chapter X), the diamagnetic susceptibility,[22] and the resonance energy. The resonance energy of 106 kcal m^{-1} determined from combustion data[23] has been replaced by a value of 84 $\pm$ 3.0 kcal m^{-1} from the work of



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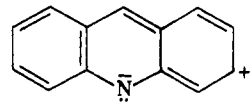

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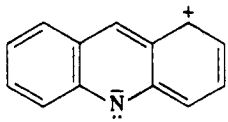

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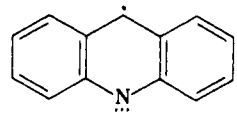

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Jackman and Packham.[24] This lower value is preferred because it is derived from bond energy values obtained from lithium aluminum hydride heats of hydrogenation.

A dipole moment of 2.09 D has been reported for acridine.[25] This suggests a shift in emphasis on the contributing structures from that implied in the earlier value[26] of 1.95 D. Leroy and his colleagues recorded an experimentally determined ionization potential of 7.78 eV for acridine.[27a] The calculated value is 7.59 eV. The n ionization potential[27b] has been found to be 2.2 eV larger than the π ionization potential, even though the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions have the same energy (3.3 eV). This implies charge redistribution, associated with $n \rightarrow \pi^*$transitions resulting from the coulombic attraction between the promoted electron and the hole it leaves behind. The molar refraction[28] was found to be 64.3.

The early calculations of π electron densities made by Longuet-Higgins and Coulson[29] by the molecular orbital method and by Pullmann,[30] using the valence bond method, have been greatly expanded by more sophisticated applications of the principles of quantum chemistry to heterocyclic molecules. To the atomic spectroscopic data[31] and proton chemical shifts[32] have been added many semiempirical parameters that have been successfully used to gain a picture of electron distribution, electron densities,[33] bond orders,[34] and reactivity indices[35] of acridines.

The X-ray diffraction studies of Phillips and his colleagues[36a,b] have provided detailed information about the crystal structure of two of the crystalline forms of acridine known as acridine III and II (see Section 3). The weighted, mean bond lengths of the two crystallographically distinct molecules in acridine II agree with those in acridine III. These two molecules exhibit significant departures from planarity, the central ring of one being the "chair" and that of the other, the "boat" form. Acridine III, monoclinic, has polar molecules arranged in antiparallel pairs, distorted slightly from planar in

ways suggestive of molecular interactions. Bond lengths and angles have been calculated. The unit cell of acridine III, $Z = 4$, has the dimensions, $a = 11.375$, $b = 5.988$, $c = 13.647$ Å, $\beta = 98°58'$. It is a modification of the anthracene structure.

2. Methods of Preparation of Acridines

There is no general method of synthesis that can be used for most acridines. The frequently used syntheses appear to be those proceeding via the 9-acridanone or 9-chloroacridine. The 9-acridanones are readily reduced to acridans, which can be oxidized to acridines. The 9-chloro compounds can be reduced to acridines. Both 9-acridanones and 9-chloroacridines are readily available from the cyclization of diphenylamine-2-carboxylic acids (Chapter III). The most direct potentially general method is perhaps the cyclization of diphenylamine-2-aldehydes and ketones, but these substances are difficult to prepare. Bernthsen's synthesis, a variation of which was used in the original preparation of acridine itself, involves the combination of diphenylamines and carboxylic acids under vigorous conditions and is useful for the synthesis of 9-substituted acridines. A similar reaction with formic acid gives 3-amino-acridines or 3,6-diaminoacridines according to the conditions employed. A related synthesis, in which the carboxylic acids are replaced by aldehydes, initially gives acridans, easily oxidized to the acridines. A small number of acridines have also been obtained from dehydrogenation, cyclodehydrogenation, and other reactions that will be considered here.

A. Preparation of Acridines from 9-Acridanones or 9-Chloroacridines

Excluding the zinc dust distillation of 9-acridanones and their reactions with Grignard and similar reagents, there are no reports of useful one-stage reductions of a 9-chloroacridine, prepared from the 9-acridanone with phosphorus oxychloride (Chapter III), and only two of 9-acridanones (p. 20 and Ref. 58b) to the corresponding acridine.

The reason for this failure is that it is much more difficult to reduce a 9-acridanone or a 9-chloroacridine to the acridine than it is to reduce the acridine to the acridan. Consequently, the reduction of a 9-acridanone (or 9-chlororacridine) gives largely the acridan in excellent yield under the proper conditions. As the quantitative oxidation of an acridan to the acridine is easily carried out, this two-stage conversion is a very valuable, frequently used procedure. Table I lists the monosubstituted acridines that have been prepared in these two-stage processes; they are representative of a much

TABLE I. Conversion of 9-Acridanones and 9-Chloroacridines to the Corresponding Acridines

Compound reduced	Procedure	Yield of acridine (%)	Ref.
9-Acridanone	Na and AmOH; CrO_3	80	53,65
	Zn dust distillation	100	8
9-Acridanone-2-carboxylic acid	Al/Hg and EtOH; $FeCl_3$	75	108
9-Acridanone-4-carboxylic acid	Al/Hg and NaOH (aq); $FeCl_3$	80	108
9-Acridanone-2-sulfonic acid	Na/Hg and water; $FeCl_3$	75	109
1-Amino-9-acridanone	Na/Hg and NaOH(aq); $FeCl_3$	70	84
	Al/Hg and EtOH	0	67
2-Amino-9-acridanone	Na/Hg, EtOH and CO_2; $FeCl_3$	85	67
	Al/Hg and EtOH; $FeCl_3$	75	67
3-Amino-9-acridanone	Na/Hg, EtOH and CO_2; $FeCl_3$	70	67
	Na/Hg and NaOH (aq); hot air	54	110
4-Amino-9-acridanone	Na/Hg, EtOH, $NaHCO_3$	46 (impure)	64
2-Aminomethyl-9-acridanone	Na/Hg, EtOH and CO_2; $FeCl_3$	50	108
2-Bromo-9-acridanone	Toluenesulfonhydrazide method	49	48
2-Bromo-9-chloroacridine	Toluenesulfonhydrazide method	52	49
4-Bromo-9-chloroacridine	Toluenesulfonhydrazide method	88	49
4-Bromo-9-chloro-1-ethylacridine	H_2 and Raney nickel, then H_2 and $Pd/SrCO_3$; CrO_3	39[a]	111
9-Chloroacridine	H_2 and Raney nickel; CrO_3	70	53, 55
	Toluenesulfonhydrazide method	73	44
	Hydrazine hydrate; O_2, Pt	55	50

(Table Continued)