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A Review on the Syntheses of the 9-Substituted Acridines (1970 - 1976)

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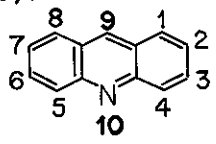
A summary of synthetic works published in the 1970s is presented. Apart from the syntheses, mechanisms of the key steps in these reactions are included as well as spectral studies and biological properties of these newly obtained compounds are mentioned.

1. Introduction

The stimulus for many investigations on the acridine chemistry carried out all over the world has come primarily from a recognition of important biological activity of these heterocyclic compounds[1]. Various acridine derivatives have been tested extensively and antibacterial[2], antimalarial[3], anthelmintic[4], analeptic[5], and recently antineoplastic[6,7] activities have been reported for many substituted acridines.

There are two chief methods of synthesis that can be used for most acridines. The direct general method is the cyclization of diphenylamine-2-aldehydes and ketones or, more seldom, Bernthsen's synthesis[8]. If diphenylamine-2-carboxylic acids are employed to the cyclization then 9-acridanones or 9-chloroacridines are easily obtained and these are undoubtedly the most frequently used intermediates in the synthesis of acridine derivatives. A large number of methods is available to convert them to the compounds required.

The overwhelming majority of reactions in the acridine syntheses, hydrolyses, or their conversions and transformations occurs at the positions 9 and/or 10 owing to the unequal distribution of electron density in the molecule and considerable flexibility of the central ring (aromaticity of the central ring is lost with relative ease).



Furthermore, substituents in positions 9 and 10 primarily determine the chemical character of the compounds and therefore the classification into main groups of acridine derivatives, e.g.,

acridines, acridans, 9-acridanones, is based on the substituents in these positions.

Hence, various research teams all over the world have been interested in the 9-substituted acridines: R. M. Acheson in the United Kingdom, A.Albert, R.H.Prager in Australia, A. Ledóchowski in Poland, B.F. Cain and G.J. Atwell in New Zealand, O. Tsuge and A. Torii in Japan, M. Ionescu in Roumania, and among Soviet authors O.N. Chupakhin, I.Ya. Postovskii and A.K. Sheinkman must be mentioned.

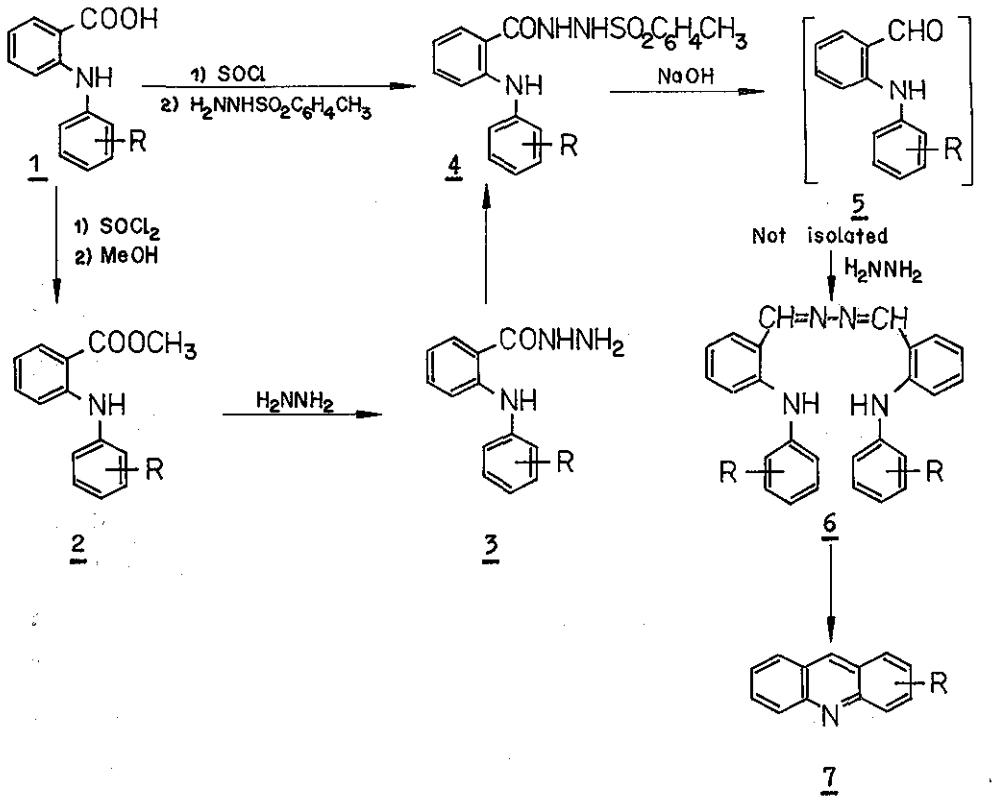
Excellent reviews are available on the acridine chemistry, especially books by A.Albert[5,9] and R. M. Acheson[10,11] and articles in German by G. Löber[12], S. Johne and D. Gröger[13], and J. Reisch, K. Szendrei, E. Minker and I. Novák[14]. The large number of recent investigations has prompted me to compile a survey of the chemical literature on this topic. Since the last textbook on acridines covers the literature up to 1969 and the aforementioned review articles to 1970 the present paper outlines the studies published in the 1970s.

The review is divided into two parts; the first one deals with synthetic works on the 9-substituted acridines and the second part will consider the kinetic studies on reactions in 9 position of these compounds. The number of publications is of such a magnitude that only the principal features and conclusions from these investigations could be outlined and only some typical examples of studies could be mentioned specifically. The special emphasis was placed on the compounds that turned out to be useful in acridine chemistry and/or industry alike.

The classification of the acridine derivatives used throughout this review is based on the substituent type in 9 position.

2. Syntheses of the acridine system

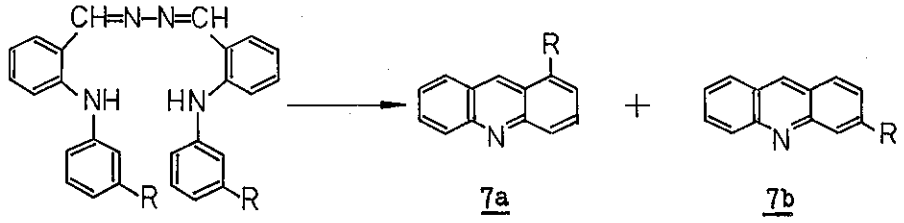
The general methods of syntheses of the acridine derivatives have been comprehensively summarized[15] and only some modifications were made in last years. A series of previously unreported acridines was obtained from diphenylamine-2-carboxaldehydes prepared *via* the McFadyen-Stevens reaction[16]. This method was earlier described by Albert[17] for the unsubstituted derivative (4) synthesized from N-phenylanthranilic acid *via* ester 2 and hydrazide 3.



Graboyes and co-workers[16] have prepared 26 derivatives of 4 ($R=CH_3$, OCH_3, Cl, Br, CF_3, and NO_2 in positions 2′, 3′, and 4′; SCH_3 and SO_2CH_3 in positions 2′ and 4′; C_6H_5 in position 2′ and C_4H_9 in 4′)

in 60-95 % yield by first converting acid 1 to its acid chloride, followed by reaction with p-toluenesulphonylhydrazine in a hydrocarbon solvent. In some cases, however, e.g., R=3-CH_3, 3-OCH_3, the route *via* the ester and hydrazide 3 turned out to be more productive. Decomposition of the p-toluenesulphonylhydrazides (4) was carried out in methyl or ethyl cellosolve with aqueous sodium hydroxide. The aldehydes 5 were not isolated because of their inconveniently low melting points and hence some difficulties with their isolation and purification. A more convenient procedure with better yields and easier isolation was to add hydrazine to the reaction mixture and thus when the aldehyde formed it was converted directly to the azine 6 which was insoluble and precipitated. In this way diphenylamine-2-carboxaldehyde azines were obtained in overall yields of 40-80 % (substituents R in the same positions as in p-toluenesulphonylhydrazides 4). The azines were readily converted to the corresponding acridines 7 by heating for a short time with concentrated hydrochloric acid. Yields were essentially quantitative in most cases[16].

When 3'-substituted azines (6a) were cyclized, ring closure could occur in either *ortho* or *para* position to give a mixture of 1- and 3-substituted acridines. When the substituent R was electron releasing (methoxy, methyl), the major products were 3-substituted acridines 7b. When the substituent was electron withdrawing (nitro), the major product was 1-substituted compound 7a.

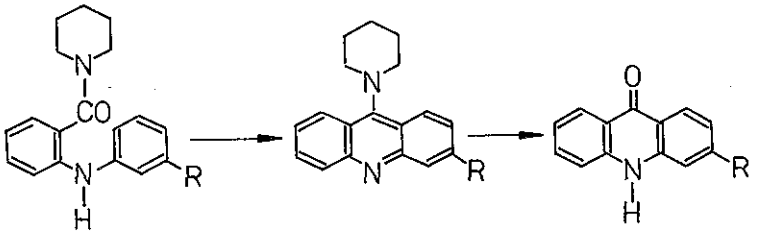


6a 7a 7b

Halogen substituents gave slightly more 1-derivatives whereas the trifluoromethyl compound gave more than a 2:1 ratio of 3-substitution to 1-substitution[16].

However, in most cases the required 9-chloroacridines are synthesized by ring closure of N-arylanthranilic acids which are in turn produced by an Ullmann synthesis[18-20]. The Ullmann reaction proceeds more smoothly if an advantageous solvent is employed. A wide variety of solvents has been used so far. More recently, Cain, Seelye and Atwell[21] have announced that the ethylene glycol monoalkyl ethers have considerable advantages as solvents. A range of such ethers with varying boiling points is commercially available, the solubility of the components in these solvents accelerates the reaction and ether miscibility with water simlifies work-up.

Moreover, it is worth to mention a few other simple modifications of the acridine system synthesis. In oredr to improve the 3 to 1 isomer ratio (these isomers are formed in the result of ring closure of the appropriate N-(3-alkylphenyl)anthranilic acids) the piperidides of the anthranilic acids (8) were used[22] instead of previously used acids. The interaction between the 3-substitu-



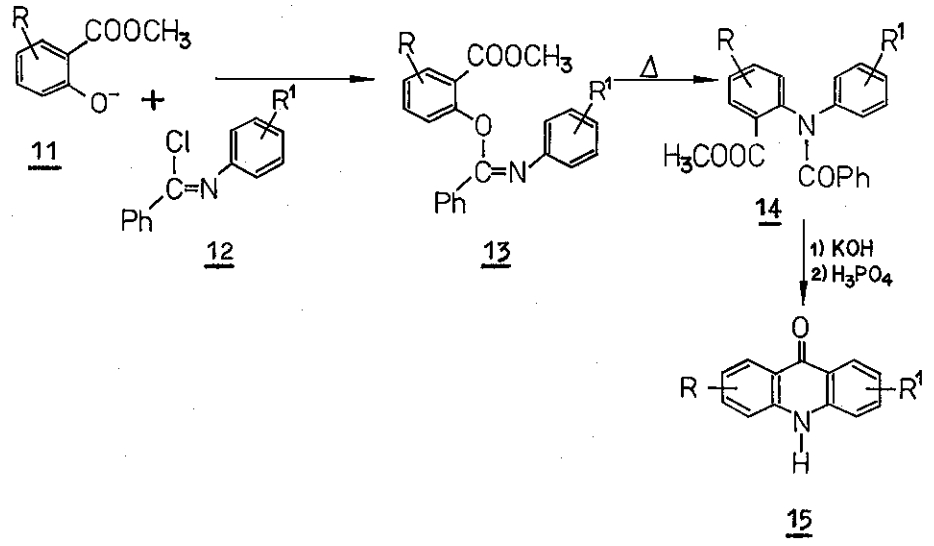
8 9 10

ent and the alkyl groups of the amide function provides a steric barrier to the formation of the 1-substituted acridine derivative and often less favoured 3-substituted isomer becomes the dominant product.

Thus, application of this reaction sequence to the preparation of the methyl analogue ($R=CH_3$) afforded 3-methylacridanone (10) in 86 % overall yield and in the case of $R=CF_3$ the yield was 87 %. In contrast, direct ring closure of the corresponding anthranilic acids is claimed to produce mixtures containing 20 % of 3- and 80% of 1-methylacridanone and 35 and 65 % of 3- and 1-trifluoromethylacridanones, respectively[22].

Separation of isomers has been avoided when possible by using unequivocal syntheses from substituted 2-chlorobenzoic acid components[21]. A different route was sometimes followed to avoid isomer formation, e.g., 3-methylacridanone was conveniently prepared, in quantitative yield, by condensation of 3-methylcyclohexanone with anthranilic acid to 1,2,3,4-tetrahydro-3-methylacridanone, followed by the dehydrogenation (Pd/C; refluxing Dowtherm A)[21].

Cain and Atwell[23,24] have also modified the Chapman rearrangement[25] to prepare 4,5-disubstituted acridine derivatives. Two

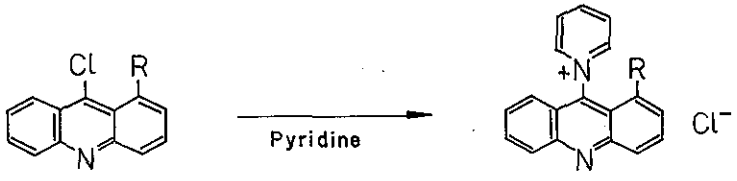


simple modifications of the above route[23] facilitated this synthe-

sis: (a) the thermal rearrangement step (13 → 14) proceeded more smoothly and cleanly in refluxing Dowtherm A, (b) the extremely strenuous hydrolytic conditions necessary for removal of the benzoyl protecting group in 14 were avoided by direct ring closure (phosphoric acid or polyphosphoric acid) of the acid resulting from saponification of the methyl ester (14).

Acridanones (15) were converted in an excellent yield to the corresponding 9-chloro compounds on treatment with thionyl chloride containing catalytic quantities of DMF[23] and thus more vigorous conditions previously used (refluxing phosphoryl chloride) were avoided.

The method of separation of 1- and 3-isomers elaborated in our laboratory was also developed to get the requisite 1-isomer in higher yield. 1-Substituted 9-chloroacridines appeared to react with pyridine much quickly and under milder conditions than their 3-isomers[26] and owing to the solubility of N-(1-substituted acridinyl-9)pyridinium chloride (17) in pyridine the undissolved 3-substituted 9-chloroacridine could be filtered off[27].



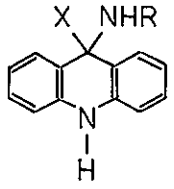
16 17

If the residual solid was additionally washed with pyridine and a few portions of organic solvents, the yield of 17 was considerably improved[28]. This method of isomer separation was also extended to the halogen substituted acridines, viz. 1- and 3-nitro-9-chloro-6-halogenoacridines[28].

3. 9-Aminoacridines

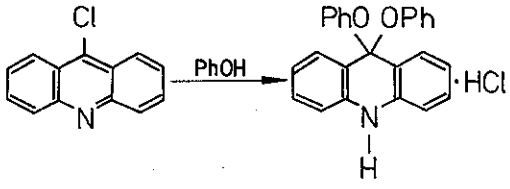
The 9-aminoacridines surely constitute one of the most important groups of the 9-substituted acridine derivatives because of their biological activity and interesting physical and chemical properties.

The synthesis of 9-aminoacridines most often involves the cyclization of an appropriately substituted diphenylamine-2-carboxylic acid, prepared by the Ullmann reaction, to the corresponding 9-chloroacridine[29]. The 9-chloroacridines, by virtue of the high reactivity of the chlorine atom, are easily converted to 9-aminoacridines. Direct condensation of aliphatic or aromatic amines with 9-chloroacridines has hitherto been the most common procedure and in recent years hundreds of new substituted 9-aminoacridines have been synthesized in this manner[21-24,30-63]. The majority of these reactions are traditionally carried out in phenol[31-50]. It is generally accepted[29] that such a condensation in phenol proceeds through structure 18. This is plausible as far as the activated complex is concerned. However, it must be emphasized that such



X=Cl,OPh,OR,SR,etc.

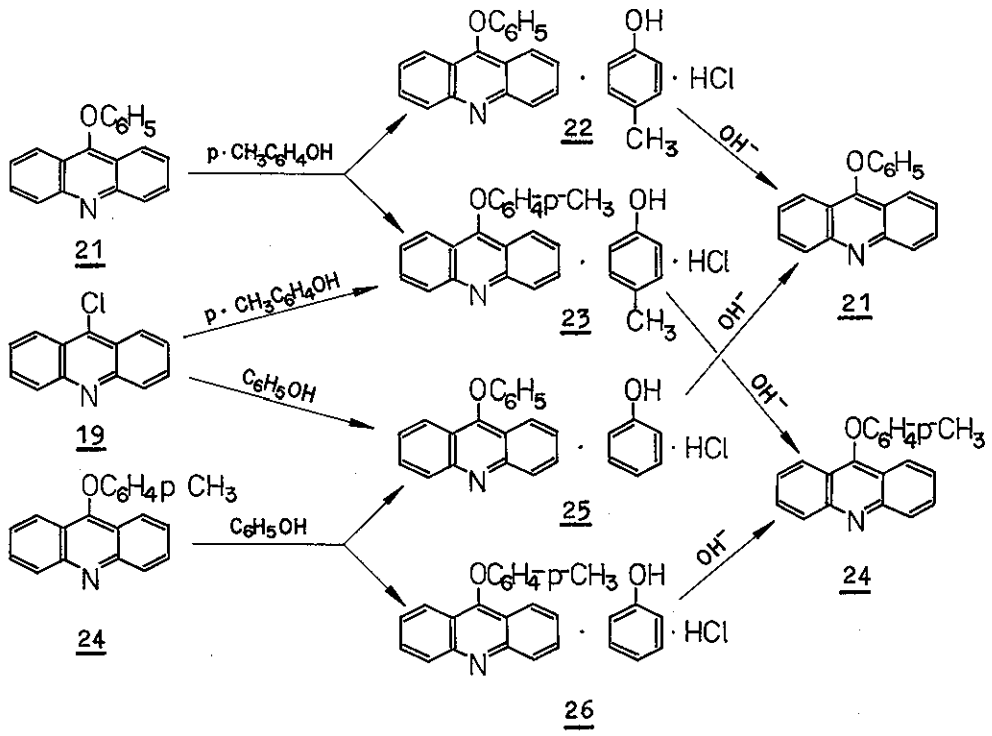
18



19 20

species of structure 18 are unstable and easily decompose giving 9-X- or 9-NHR-acridines unless they are stabilized by alkylation in position 10 or by introduction of sufficiently bulky substituents on the 9-amino group, e.g., R=alkyl, aryl, etc.

In order to gain insight into the nature of the compound isolated by Drozdov and Cherntzov[64] as the product of reaction of 9-chloroacridine (19) with phenol which has been considered hitherto to be 9,10-dihydro-9,9-diphenoxyacridine hydrochloride (20), the crossover experiment was performed according to the following scheme[65]:

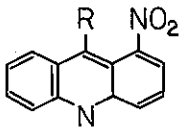


Compounds 22, 23, 25 and 26 were isolated and their NMR and UV spectra were used to study their structure. The products found in the course of the above reaction sequence, the data obtained from spectroscopic investigations and other premises[65,66] indicate that these compounds are not of the acridan type (20) but are 9-phenoxyacridine hydrochlorides complexed with the phenol moiety which can be easily removed or replaced without a change

of the substituent in position 9 of the acridine nucleus. Moreover, acridan is known as a very weak base (pK_a=-0.93) and it is hard to understand that the salt of acridan derivative could be stable in the phenol medium (pK_a of phenol is ca. 10). In the light of these facts, the hypothesis of the existance of 20 is untenable.

The 9-aminoacridine derivatives, prepared in last six years, are summarized in Table 1 and Table 2. Of other 9-aminoacridines obtained from the corresponding 9-chloroacridines in phenol, the following should be mentioned.

Ledóchowski and co-workers[33-37] have obtained a series of 1-nitro-9-alkylaminoacridines (27: R=NHC_6H_5, $NHCH_2C_6H_5$, N$(CH_2)_5$, $NH(CH_2)_4NH$(1-NO_2-acridyl-9), and $NH(CH_2)_4NH_2$)[35], 1-nitro-10-me-



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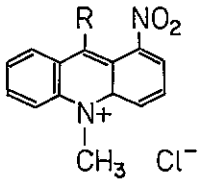

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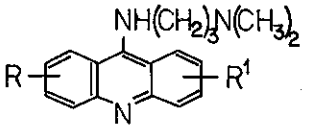
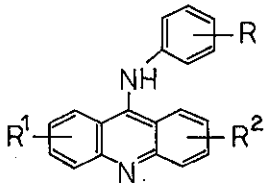


29

thyl-9-aminoacridinium derivatives (28: R= NH(1-NO_2-10-CH_3-acridanone), $NH(CH_2)_3N(CH_3)_2$, $NH(CH_2)_2CH_3$, and NHC_6H_5)[35], halogen derivatives (29: R=F,Cl,Br,I,CF_3 in positions 1 and 3; R^1=H)[36] and disubstituted acridines (29: R=1- and 3-NO_2; R^1=6-Br and 7-OCH_3)[37]. Some of these derivatives exhibit high anticancer action and particularly strong activity was revealed by 1-nitro-9-alkylaminoacridines. One of them, viz. 29 (R=1-NO_2 and R^1=H), NCS 247561, has already been introduced to therapy as an effective drug (known under the trade name Ledakrin or Nitracrine) in some tumour diseases.[67]

Cain, Atwell and others[21-24,30-32] have prepared a series of ca. 340 multiply substituted acridines of general formula 30. These compounds were evaluated in the L1210 leukemia system and one of

them, viz. 30 (R^1=R^2=H, R=p-$NHSO_2CH_3$), NSC 156303, *m*-AMSA, showed anticancer activity in screening systems and is expected to receive clinical trial[31].



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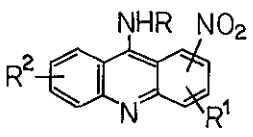
It is worth to note that 1-substituted 9-aminoacridines are active against various tumours in animals, principally sarcoma 180, whereas these are reported to be inactive against L1210 and vice versa, 3-substituted 9-alkylaminoacridines are less active against the former tumour but much more active against the latter cancer[32].

A few compounds of structure 30 have also been prepared by Egyptian workers[68] and Soviet team: 30 (R^1=1-, 2-, 3- and 4-OCH_3; R^2=6-NO_2)[41,42], (R^1=1-NO_2, R^2=H)[43] and (R^1=4-NO_2, R^2=H)[44]. Other authors have been engaged in syntheses of other nitroacridines: 31 (2-NO_2, R^1=3-Cl, R^2=7-Cl)[45] and 31 (5-NO_2, R^1=H, R^2=1-, 2-, 3- and 4-OCH_3)[46]. Some of these compounds reveal high activity against bacteria[41-46].



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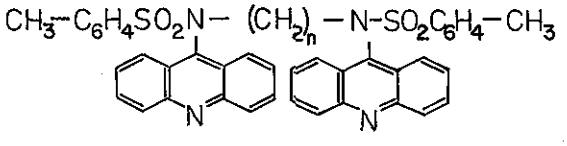
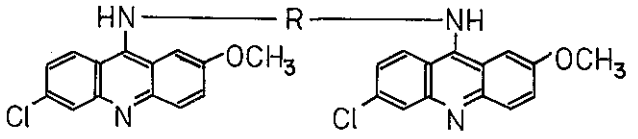


32

A series of N,N′-bis-(9-acridinyl)polymethylenediamines (32) has been prepared[47]. The synthesis was achieved by condensation of 9-chloroacridine with different diamines H_2N-$(CH_2)_n$-NH_2, n = 1 to 12, and then the free bases derived from them were condensed with p-toluenesulphonyl chloride to give 32.

Compounds of similar structure, 33, with various alkyl or alkylaminoalkyl chains (R) have been obtained either directly from 9-chloroacridine and a free amine or from 9-phenoxyacridine and the amine hydrochloride in phenol[48].



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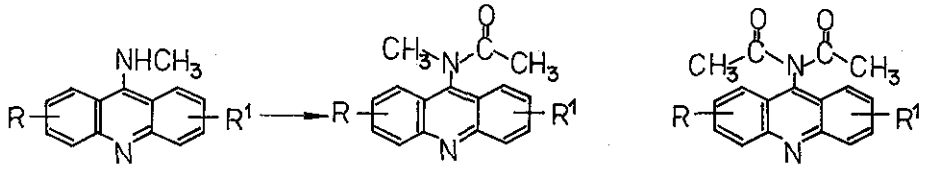
9-Phenoxyacridine is second best acridine derivative employed in the condensation with amines and is most conveniently prepared by the action of phenol on 9-chloroacridine. Gaidukevich et al.[53-57] have followed this way to get 9-methylaminoacridines having substituents on the aromatic ring (34).



34 35 36

These were treated with acetic anhydride to give the corresponding 9-(N-methyl-N-acetylamino)acridines (35: R=H,Cl,OCH_3; R^1=6-NO_2)[53], (35: R=CH_3,Cl, and OCH_3 in positions 2 and 4; R^1=7-NO_2)[54], (35: R=2-CH_3,2-Cl,4-CH_3,4-Cl; R^1=6-NO_2)[55] and (35: R=H; R^1=CH_3, Cl, and OCH_3 in positions 2 and 4)[56]. The acetylation of 9-aminoacridines bearing the unsubstituted amino group under similar conditions yielded the corresponding 9,9-diacetylaminoacridines (36)[53] while the reaction of 9-aminoacridines with N-acetylglutamic acid anhydride gave the acetylated compound 37. However, in case of the reaction of unsubstituted 9-aminoacridine with the latter acylating agent, the rearrangement of N-acetylglutamic acid anhydride occurred to give N-acetylpyroglutamic acid and compound 38 was found to be the final product[58].

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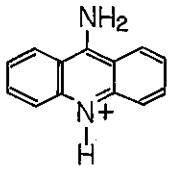

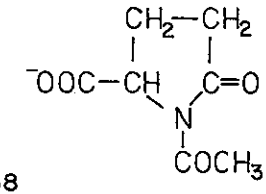

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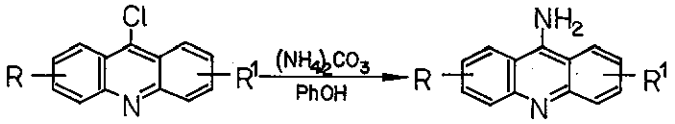
All these compounds were tested in pharmacological experiments and the 9-amino derivatives were found to be useful as bactericides[55] whereas the 9-acetamino acridines were inactive[54]. Compound 38 was proved to act bactericidally in the presence of benzylpenicillin[58].

The 9-aminoacridine derivatives (40) substituted in the acridine ring were prepared from the appropriate 9-chloroacridines (39) and ammonium carbonate in phenol[60,69]. In this way 2-, 3-, and



39 40

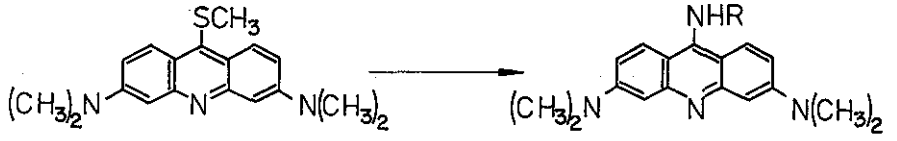
4-methoxy-9-amino-7-sulphodimethylaminoacridines (40: R=7-$SO_2N(CH_3)_2$ R^1=2-, 3-, 4-OCH_3)[69] and 2-s-butyl-, 2-t-butyl-, 4-ethyl-, 2,7-di-t-butyl- and 2-s-butyl-9-amino-6-nitroacridines[61] were synthesized.

Following the recognition of the acid catalysis of the condensation reactions of 9-chloroacridine with amines, these reactions were successfully carried out in other solvents, e.g., in an excess of the reacting amine[50]; in aqueous ethanol[21] or absolute ethanol[70] with a few drops of concentrated hydrochloric acid; in absolute methanol[61], absolute ethanol[21], absolute 2-ethoxyethanol[21] or N-methylpyrrolidine[22] with a few drops of methanesulphonic acid. More recently, 9-amino-2-ethoxy-6-nitroacridine was reported to be formed by a condensation of the 9-chloroacridine derivative with urea

in a polar organic solvent (ethylene glycol) in the presence of salts (ammonium chloride) and catalytic amount of mono- or polyhydroxy compounds (resorcinol) and then it was reduced with iron to give 6,9-diamino-2-ethoxyacridine[71]. The latter compound, known as rivanol and useful as a gastointestinal agent having bactericidal effect, was mixed with cellulose in water or alcohols to give crystal powder of 6,9-diamino-2-ethoxyacridinecarboxymethylcellulose complex without any bitter taste[72].

Quinacrine hydrochloride turned out to be another preparative source of the 9-aminoacridine derivative. In 1936 quinacrine was reported to undergo degradation under acidic conditions giving a mixture of 2-methoxy- and 2-hydroxy-9-amino-6-chloroacridines[73]. When this reaction was carried out in 48 % hydrobromic acid, the requisite 2-hydroxy component was isolated as the only product in 88% yield of pure compound after recrystallization from alcohol[74]. Chromatographic methods have also been developed for the analysis of the products of the above degradation reaction[75].

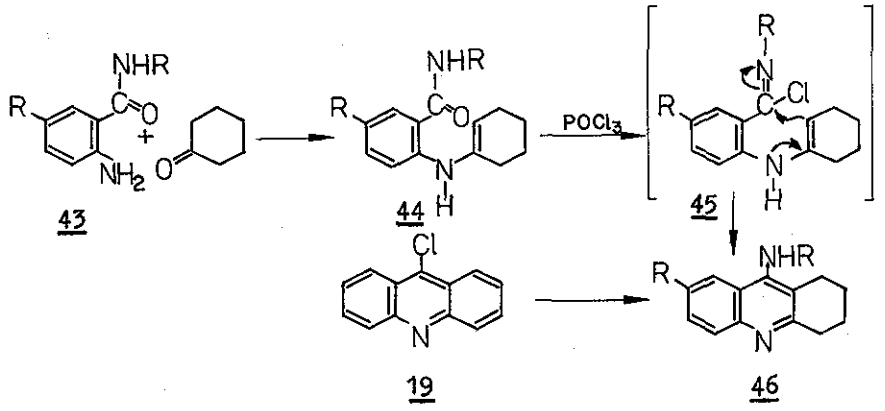
Two 9-amino-3,6-bis(dimethylamino)acridine derivatives (42) were prepared from 9-methylthio-3,6-bis(dimethylamino)acridine



41 42

(41) and alkyl or aromatic amines in phenol[76]. Several mono(dimethylamino)-9-alkylaminoacridines [$N(CH_3)_2$ in positions 2 or 3] were also prepared by these authors[76] from the 9-chloroacridine derivatives and alkylamines in phenol.

Konshin[77-82] has investigated the synthesis of 9-arylamino-1,2,3,4-tetrahydroacridines (47) according to the following scheme:



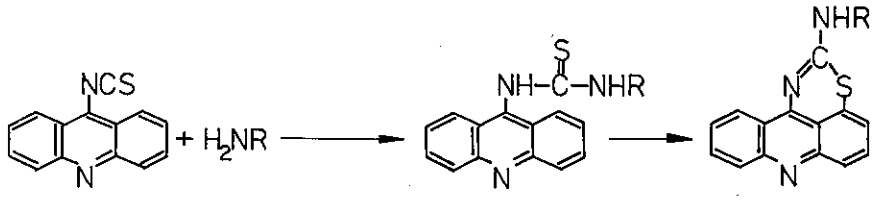
43 44 45 19 46

The condensation of anthranilamides 43 with cyclohexanone gave the enamines 44, which, on treatment with phosphoryl chloride, yielded the tetrahydroacridine 46 (R=H, Cl, Br) *via* the chloramides 45[81]. The structure of compound 46 (R=H) was confirmed by an alternative synthesis from 9-chloro-1,2,3,4-tetrahydroacridine and additionally by IR spectra[81].

Of other 9-substituted acridines containing the C^9-N bond, 9-isothiocyanato-, 9-azido- and 9-hydrazinoacridines are most important. Acridine-9-isothiocyanate (47) has been found useful for the detection of trace of penicillin[83] and therefore attracted a great deal of attention in the evaluation of fluorescent isothiocyanate compounds. It has been prepared from 9-chloroacridine and silver thiocyanate[84]. Later this method was modified by use of potassium thiocyanate[85] and higher yields (88 %) were observed as compared with the previous procedure (58 %).

Reaction of acridine-9-isothiocyanate (47) with amines in alcohol yields a mixture of fluorescent compounds[84]. Since the fluorescence of this mixture of products could be related to the concentration of the amine used, the procedure was applied after some modifications[86] as an analytical method to primary and secondary amines[60] with special emphasis on compounds of biological

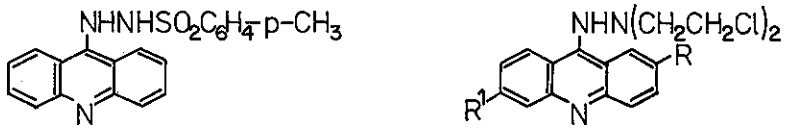
significance. It was subsequently recognized[75] that the main fluorescent product was a cyclized compound 49 produced by photo-oxidation of the thiourea 48.



47 48 49

Compounds 48 can be alternatively obtained from 9-aminoacridine and alkyl or aryl isothiocyanates in boiling acetone[51]. Several compounds of formula 48 are listed in Table 1.

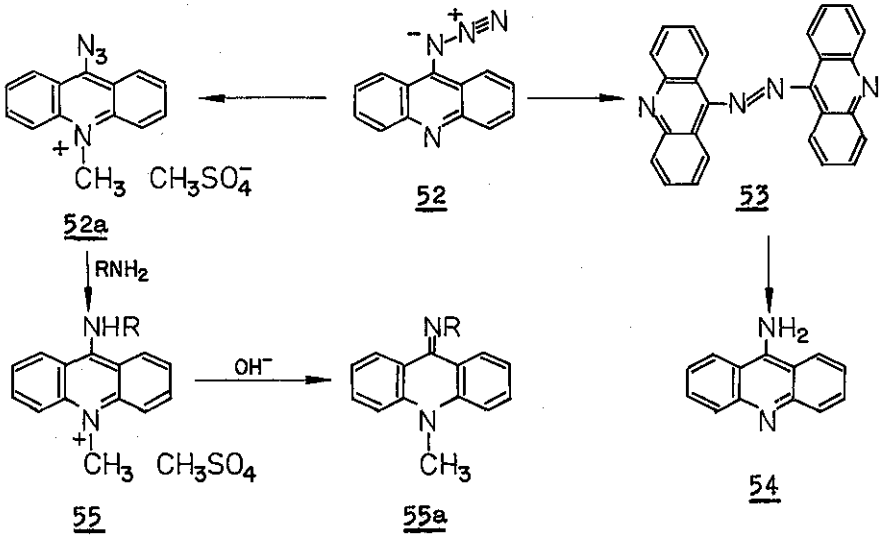
As far as the 9-hydrazinoacridines are concerned, the fact that the hydrazide group can be easily removed from 50 has been widely used since its discovery in the reduction of 9-chloroacridine by first conversion to a 9-arylsulphonylhydrazone 50 followed by treatment with base. This method was followed to prepare 2-chloroacridine[87], 2- and 4-methoxyacridines[88] and 1,2,3-trimethoxyacridine[89]. The decomposition of these derivatives of 50 was accomplished on boiling in alkaline glycol.



50 51

Synthesis of 9-[N,N-bis(2-chloroethyl)hydrazino]acridine and its derivatives (51: R=H, OCH_3, OC_2H_5; R^1=H, Cl, NO_2) has also been reported[90]. These compounds are found to inhibit the growth of some experimental tumours[90].

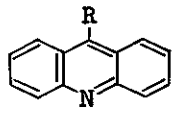
9-Azidoacridine (52) has been synthesized from 9-hydrazinoacridine and sodium nitrate in 2N hydrochloric acid[91] or from 9-chloroacridine and sodium azide in refluxing aqueous acetone[92].

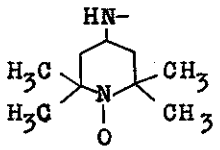
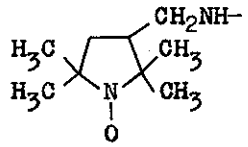
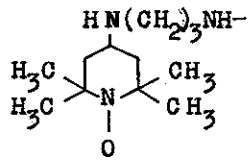


It decomposed violently at 150° affording a red solid consisting of substantial amounts of 9,9'-azoacridine (53). Controlled decomposition in o-dichlorobenzene or nitrobenzene gave pure azocompound in 70 % yield. Photolysis of 9-azidoacridine also afforded azoacridine in 81 % yield. The structure of azoacridine (53) was confirmed by an alternative synthesis and by its reduction to 9-aminoacridine (54)[91].

Interaction of 9-azidoacridine (52) with dimethyl sulphate in dry benzene yielded 9-azido-10-methylacridinium methyl sulphate (52a). The quaternary salts (55: R=Ph, sec-Pr, 2-pyridyl) were formed when 52a was stirred with the appropriate amines. Compounds 55 were characterized as the anils (55a) which were deposited when the crude salts (55) were basified with aqueous ammonia[91].

Table 1. 9-Aminoacridine derivatives.

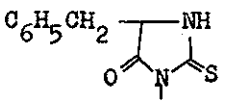
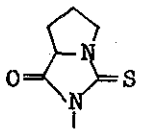
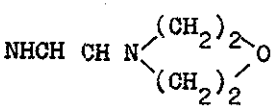


R	M.p. °C	Recrystn. solvent	Yield %	Procedure	Ref.
	188-190	$CHCl_3$-heptane	30	4-amino-2,2,6,6-tetramethyl-1-piperidine N-oxide and 9-chloroacridine	62
	190-191	$CHCl_3$-heptane	36	3-aminomethyl-2,2,5,5-tetramethyl-1-pyrrolidine N-oxide and 9-chloroacridine	62
	122-124	$CHCl_3$-heptane	20	N-[4-(2,2,6,6-tetramethyl-1-piperidine N-oxide)]-1,3-diaminopropane and 9-chloroacridine	62
$NHCOOC_2H_5$	192-193	EtOH-H_2O	92	9-aminoacridine and ethyl chloroformate	51
NHCOO-n-C_4H_9	147-148	EtOH-H_2O	92	9-aminoacridine and butyl chloroformate	51

(Table Continued)

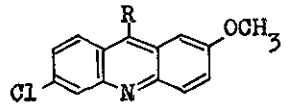
Table 1. (Continued)

R	M.p. °C	Recrystn. solvent	Yield %	Procedure	Ref.
$NHCONHC_6H_4$-p-OCH_3	228-229	EtOH-H_2O	95	9-aminoacridine and p-methoxyphenyl isocyanate	52
$NHCONHC_6H_5$	189-191	EtOH-H_2O	95	9-aminoacridine and phenyl isocyanate	52
$NHCOOCH_2C_6H_5$	210-213	EtOH-H_2O	80	9-aminoacridine and benzyl chloroformate	51
$NHCOOCH_2CH(CH_3)CH_3$	152-154	EtOH-H_2O	80	9-aminoacridine and 2-methylpropyl chloroformate	51
$NHCSNHCH_2C_6H_5$	178-180	EtOH-H_2O	90	(a) 9-aminoacridine and benzyl isothiocyanate	51
	178-180	25%EtOH-H_2O	80	(b) acridine-9-isothiocyanate and benzylamine	
$NHCSOC_2H_5$	160-162	EtOH-H_2O	90	acridine-9-isothiocyanate and absolute ethanol	51
$NHN(CH_2CH_2Cl)_2$	251.5	EtOH	27	9-chloroacridine and N,N-bis(2-chloroethyl)hydrazine	90
NCS	129	acetone	88	9-chloroacridine and potassium thiocyanate	59
$NHCSNHC_4H_9$	180-181	95 % EtOH	84	acridine-9-isothiocyanate and n-butylamine	59
$NHCSNHC_6H_5$	178-180	absolute EtOH	90	acridine-9-isothiocyanate and aniline	60
$NHCSNHCH_2COOH$	182-183	MeOH	55	acridine-9-isothiocyanate and glycine	60
$NHCSN(C_2H_5)_2$	184-186	absolute EtOH	76	acridine-9-isothiocyanate and diethylamine	60

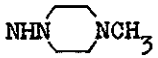
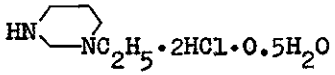
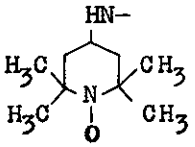
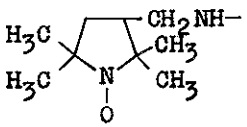
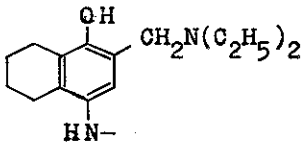
$NHCSOC_2H_5$	138-140	acetone	50	acridine-9-isothiocyanate and ethanol	60
	176-178	MeOH	13	acridine-9-isothiocyanate and phenylalanine	60
	191-193	MeOH	15	acridine-9-isothiocyanate and proline	60
$NH(CH_2)_2C_6H_4$-p-$Si(CH_3)_3$	232-235	MeOH, EtOH, EtOH-$CH_3COOC_2H_5$	96	9-chloroacridine and 1-amino-2-(p-trimethylsilylphenyl)ethane	38
p-$(CH_3)_3SiC_6H_4CH(CH_2)_3N(CH_3)_2$·HCl (HN–)	175-176	MeOH, EtOH, EtOH-$CH_3COOC_2H_5$	89	9-chloroacridine and 1-amino-4-dimethylamino-1-(p-trimethylsilylphenyl)butane	38
$C_6H_5CH(CH_2)_3N(CH_3)_2$·HCl (HN–)	216-218	MeOH, EtOH, EtOH-$CH_3COOC_2H_5$	86	9-chloroacridine and 1-amino-4-dimethylamino-1-phenylbutane	38
$NHCH_2CH_2SCH_3$	268-269	MeOH-H_2O-NaCl	68	9-chloroacridine and 2-methylthioethylamine	32
	282-283	MeOH-H_2O-NaCl	54	9-chloroacridine and ethyl-2-(morpholin-1-yl)-amine	32
CH_3NCOCH_3	225	95 % EtOH	84	9-methylaminoacridine and acetic anhydride	56
HNC_6H_4-p-$NHSO_2CH_3$·HCl*	304 (decomp.)	H_2O-EtOH	?	9-chloroacridine and p-aminomethanesulphonanilide	32

*A number of other derivatives of 9-anilinoacridine have been prepared (cf. Refs. 21-24, 30-32).

Table 2. 2-Methoxy-6-chloro-9-aminoacridines.

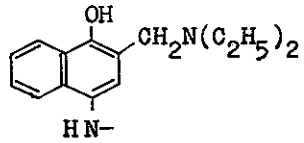
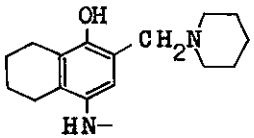
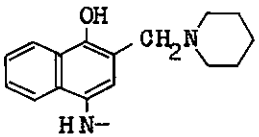


R	M.p. °C	Recryst. solvent	Yield %	Procedure	Ref.
NHCH(CH$_3$)C(H)=C(H)CH$_2$N(C$_2$H$_5$)$_2$·2HCl	240-241 (decomp.)	EtOH	16	A	49
NHCH(CH$_3$)C(H)=C(H)CH$_2$N(C$_2$H$_5$)$_2$·2HCl	249-250 (decomp.)	MeOH-EtOH	70	A	49
NHCH(CH$_3$)C≡CCH$_2$N(C$_2$H$_5$)$_2$·2HCl	225-226 (decomp.)	EtOH-i-PrOH	50	A	49
NH(CH$_2$)$_2$C$_6$H$_4$-p-NO$_2$	150-151	MeOH	82	B	60
NH(CH$_2$)$_2$C$_6$H$_4$-p-NH$_2$	130-131	80 % EtOH	76	Reduction of the preceding compound	60
NH(CH$_2$)$_2$C$_6$H$_4$-p-NCS	184-185	MeOH	?	thiophosgene and the preceding compound	60
NH(CH$_2$)$_3$C$_6$H$_4$-p-NO$_2$	229-231	MeOH	91	B	60
NH(CH$_2$)$_3$C$_6$H$_4$-p-NCS	132-133	cyclohexane	47	thiophosgene and the product of reduction of the preceding compound	60
NH(CH$_2$)$_2$C$_6$H$_4$-p-Si(CH$_3$)$_3$	265	MeOH, EtOH	94	A	38
p-(CH$_3$)$_3$SiC$_6$H$_4$CH(CH$_2$)$_3$N(CH$_3$)$_2$ HN—	300	MeOH, EtOH, EtOH-H$_2$O	90	A	38
C$_6$H$_5$CH(CH$_2$)$_3$N(CH$_3$)$_2$·HCl HN—	223-225	MeOH, EtOH, EtOH-H$_2$O	91	A	38

$NHN(CH_3)CH_2CH_2N(CH_3)_2$	225-226 (decomp.)	cyclohexane	30	A	49
$NHN(CH_3)(CH_2)_3N(CH_3)_2 \cdot HCl$	233-235 (decomp.)	i-PrOH	17	A	49
$NHN(C_2H_5)(CH_2)_2N(CH_3)_2 \cdot 2HCl$	238-240	i-PrOH	18	A	49
	123 (decomp.)	EtOH-petroleum ether	64	A	49
	285-288 (decomp.)	EtOH	22	A	49
	197-198	$MeOH-H_2O$ (95:5)	?	A	62
	181.5-183	$CHCl_3$-heptane	?	A	62
	300	EtOH	76	A	63

(Table Continued)

Table 2. (Continued)

R	M.p. °C	Recryst. solvent	Yield %	Procedure	Ref.
	above 300	glacial acetic acid	76	A	63
	above 300	EtOH	47	A	63
	above 360	EtOH	41	A	63
NHC_6H_5	300-301	95 % EtOH	?	A	40
NHC_6H_4-p-COOH	335-337	95 % EtOH	?	A	40
$NHCOCH_2CH_2CHCOOH$ $NHCOCH_3$	237	EtOH	16	9-aminoacridine and N-acetyl-glutaminic acid	58

Method A: 6,9-Dichloro-2-methoxyacridine and required side-chain amine were used.

Method B: 6-Chloro-2-methoxy-9-phenoxyacridine and side-chain amine were used.

4. 9-Alkylacridines

The insertion of alkyl and/or aryl groups into acridine does not greatly change its properties with the only exception of the 9-substituted derivatives. 9-Alkylacridines are of particular interest because of the great reactivity of the α-hydrogen atoms on the alkyl group, due to the electron attracting properties of the acridine moiety.

The direct alkylation methods of aromatic and heteroaromatic compounds were reviewed by French authors[93] in 1971. However, the benzylacridines described in that paper were prepared in the 1950s.

Recently, Italian workers[94] have extensively studied aromatic homolytic alkylation of protonated heterocyclic bases including pyridine[95], quinoline[96] and acridine[97]. The nucleophilic character of alkyl radicals permits the ready and selective alkylation of these bases. They have used a variety of radical sources[97]: oxaziranes, hydroperoxides, acylperoxides, carboxylic acids and lead tetracetate, and more recently, silver-catalysed oxidative decarboxylation of carboxylic acids with peroxydisulphate. The last method, based on the findings of other authors[98], is particularly noteworthy because of the good yield and the high selectivity obtained. The catalytic action of the silver salt takes place according to the following redox radical chain:

$$2\ Ag^{+} + S_2O_8^{--} \longrightarrow 2\ Ag^{++} + 2\ SO_4^{--}$$

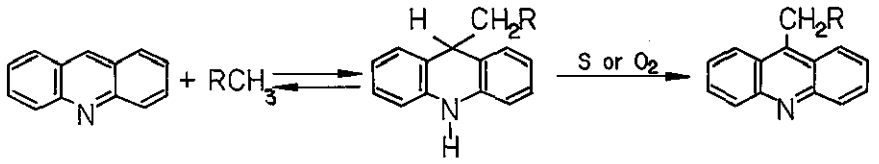
$$RCOOH + Ag^{++} \longrightarrow R\cdot + CO_2 + H^{+} + Ag^{+}$$

The addition of the alkyl radical (R = methyl, ethyl, isopropyl, butyl) to the protonated acridine is reported to be quantitative[97].

Synthetic reactions of phenylsulphonylcarbanion with acridine and other aromatic compounds were studied by Yamamoto, Nisimura and Nozaki[99]. They have summarized the investigations of the aromatic methylation with sulphinyl- and sulphonylcarbanions and discussed the reaction paths.

Finally, the photoreaction of acridine with trialkylboranes in benzene was studied[100]. 9-Butyl- and 9-cyclohexylacridines were obtained in this manner in 8 and 5 % yield, respectively.

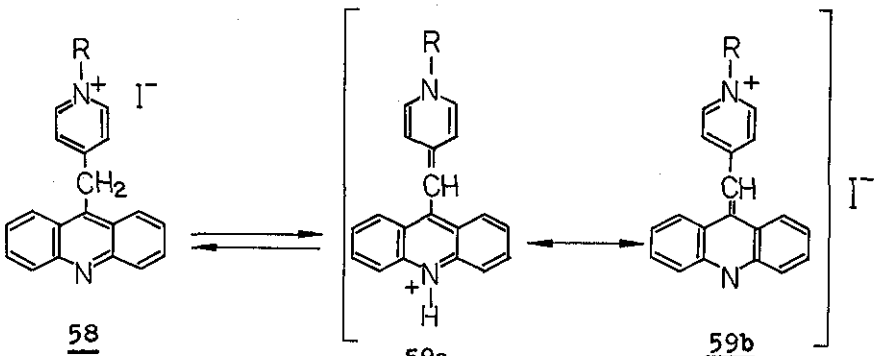
To the above methods involving direct alkylation of unsubstituted acridine, the following could be added. The Soviet investigators[101] reported the formation of compounds 57 (R = 2- and 4-pyridinyl, 2- and 4-quinolinyl, and 2-benzothiazolyl).



56 57

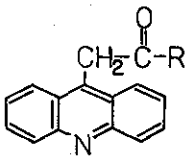
These derivatives were prepared from acridine and the appropriate components in liquid sulphur or in DMF in the presence of sulphur[101]. Acridine was also condensed with the N-alkyl-γ-picolinium iodide in DMF in the presence of oxygen to give 4-(9-acridinylmethyl)pyridinium iodide (58: R=CH_3,C_2H_5,C_3H_7)[102]. Tautomerization of 58 to the acridinium iodide 59a was extensive in DMF, ethanol and chloroform solutions as determined by UV spectroscopy[102].

The mechanism of the aforementioned condensation was also studied and the reaction was suggested[103] to proceed through intermediates such as 56, though no traces of 56 were detected in IR or UV spectra.



58 59a 59b

A few papers deal with the preparation of compounds of general formula 60. Acridine reacted with ketones (CH_3COR: R = C_6H_5, C_6H_4-p-CH_3) in the presence of aluminium and Hg^{2+} salts to give the corresponding 60 in 35-60 % yield[104]. A series of 9-phenacylacridines and other acridine ketones (60: R=C_6H_5, C_6H_4-p-CH_3, 2-ketocyclopentanyl) has also been prepared from acridine and the



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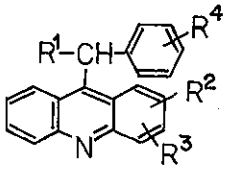


61

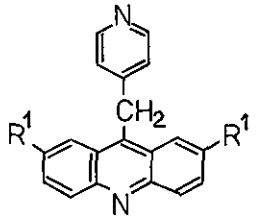
appropriate ketones in DMF in the presence of benzoyl chloride[105-109] and mechanism of this kind of the Reissert reaction as well as that of acridine N-oxide with diketene giving 9-acetonylacridine (60: R=CH_3)[109] have been discussed.

All the aforementioned papers describe the syntheses of 9-alkylacridines starting from unsubstituted acridine[93-109]. In some cases, however, it is desirable to employ 9-substituted derivatives. Of these, the starting material used most frequently is again 9-chloroacridine. Thus, condensation of 9-chloroacridine with

p-Cl-C_6H_4-$CH_2CO_2CH_3$ in DMF in the presence of sodium hydride followed by heating with NaOH-H_2O-CH_3OH and acidification with hydrochloric acid afforded p-chlorobenzylacridine (61: R^1=R^2=R^3=H, R^4=Cl)[110]. Thirty four substituted benzylacridines were obtained in this manner (61: R^1=H, $COOCH_3$; R^2=H, 2-OH, 2-OCH_3; R^3=H, 3-OH, 3-OCH_3, 4-OCH_3; R^4=Cl, OCH_3, $(OCH_3)_2$, $(OH)_2$, $(CH_3)_2$, etc.)[110].

9-Chloroacridine and its derivative, 9-chloro-2-ethoxy-6-nitroacridine, were successfully condensed with 2- and 4-picoline as well as 2- and 4-methylquinoline to afford the corresponding compounds of formula 57, some of which revealed pharmacological activity[111].

It was already mentioned above that acridine reacted with heterocyclic compounds containing an active methyl group giving 9-substituted acridines[101]. It appeared that in case of 2- and 4-picolines there would be also other possible reaction paths. The 9-chloroacridine derivatives were found to react with 4-picoline to give 62 (R^1=H, Br) which reacted with 9-chloroacridine or its derivative in absolute butanol in the presence of trimethyl amine yielding the corresponding derivatives of 63 (R^1=H,Br; R^2 = 9-acridinyl, 1-nitro-9-acridinyl, 2,7-dibromo-9-acridinyl)[112]. Hence, it turned out that 4-picoline could react either at the methyl group or at the nitrogen atom.



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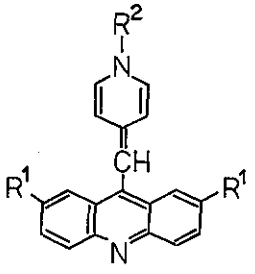

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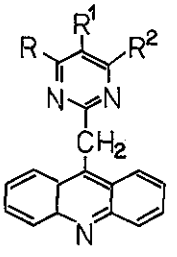
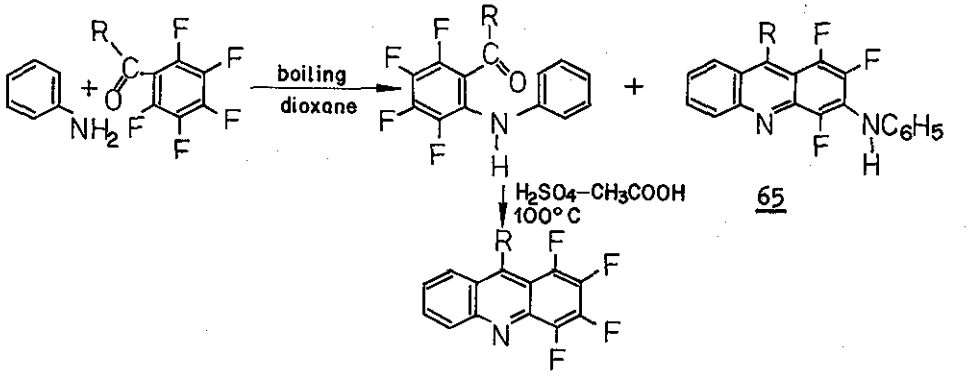


64

Syntheses of 9-(2-pyrimidylmethyl)acridines (64: R=OH, R^1=H, R^2=CH_3; OH,NO_2,H; and Cl,H,CH_3, respectively) were achieved starting from acridinyl-9-acetamide and acetoacetic ester[113]. Spectroscopic properties of these compounds (64) were also studied[114].

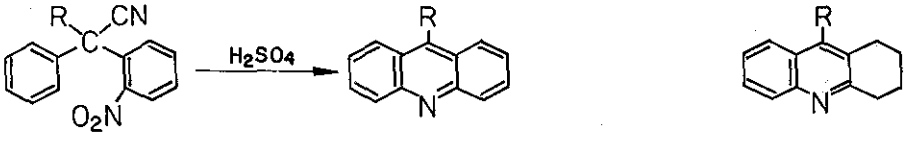
There are several reports concerning the synthesis of 9-alkyl and 9-arylacridines connected with syntheses of acridine system. Thus, compounds 65 (R=CH_3,C_6H_5,CF_3) and 9-substituted 1,2,3,4-tetrafluoroacridines (66) have been synthesized according to the following scheme[115]:



65

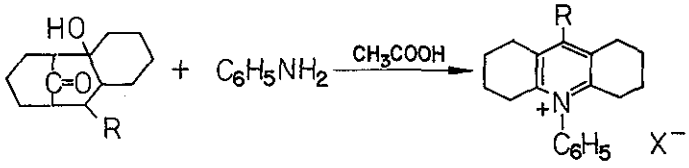
66

The 9-alkylacridines (68: R=CH_3,C_2H_5,C_6H_5) were obtained in the result of cyclization of o-nitrophenyl derivatives of phenylalkanonitriles (67) in 90 % sulphuric acid[116]. Similarly, 1,2,3,4-tetrahydroacridines (69) were prepared from cyclohexanone anil and nitriles (RCN, R=CH_3 or C_3H_7) *via* chelate compounds of boron followed by heating with hydrochloric acid in butanol and then treatment with sodium bicarbonate[117].



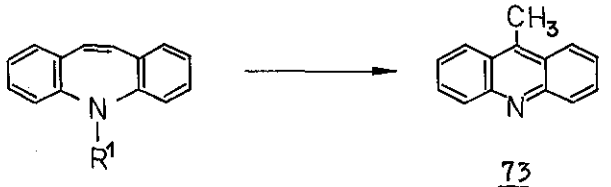
67 68 69

Interaction of 2,3-tetramethylene-4-R-bicyclo [3.3.1] nonanon-9-ol-2 (70) with aniline in acetic acid yielded 71 (R=H, CH_3, C_6H_5, α-furyl; X=ClO_4, I)[118]. Other syntheses leading to the 9-arylacridines will be considered in the following Chapter.



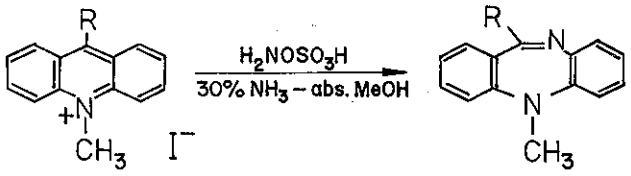
70 71

9-Methylacridine is a product of ring contraction of azepine 72 (R^1=NO, $CONH_2$) in the course of acid-catalyzed, thermal and photochemical reactions[119,120]. The yield of the product is dependent on the reaction conditions, particularly the presence or absence of oxygen and the nature of the solvent used[119].



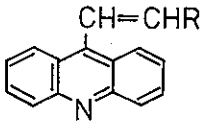
72 73

The opposite reaction to the preceding one is also known and widely used in the synthesis of the azepine derivatives and analogues. Thus, 9-methylacridine[121] and its 2-chloro[122] and 3-chloro[123] derivatives were converted to the corresponding derivatives of 72. Hirobe and Ozawa[124] have reported a novel one-step synthesis of 5H-dibenzo [b,e] [1.4] diazepine derivatives (74b: R=H, C_6H_5, CH_3) involving a ring expansion from acridinium salts (74a) by use of hydroxylamine-O-sulphonic acid. A suggested mechanism[124] involves nucleophilic attack of this acid at the 9 position of acridine[125].



74a 74b

9-Methylacridine (73) reacts also with aromatic aldehydes in DMF in the presence of benzoyl chloride to give the vinyl derivatives of acridine (75) and related chalcones (75a)[126]. This reaction can be also carried out in acetic anhydride in the absence of acyl chlorides but the yields of 75 and 75a are lower.



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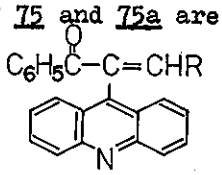
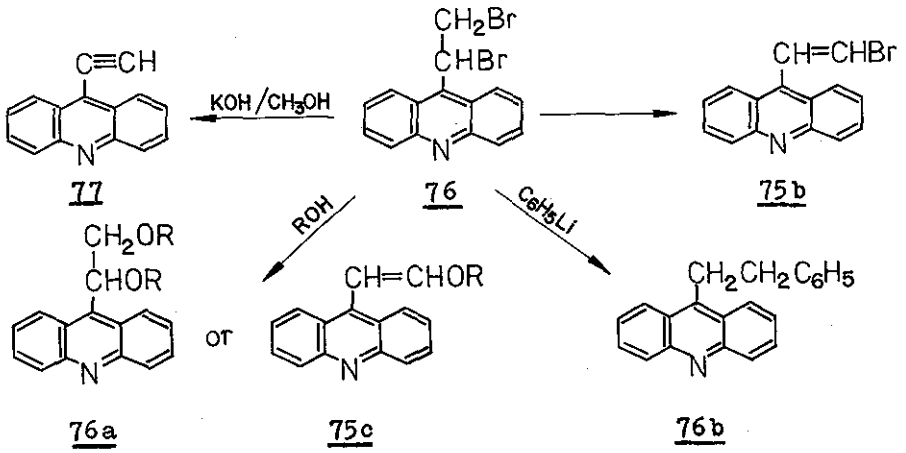


75a

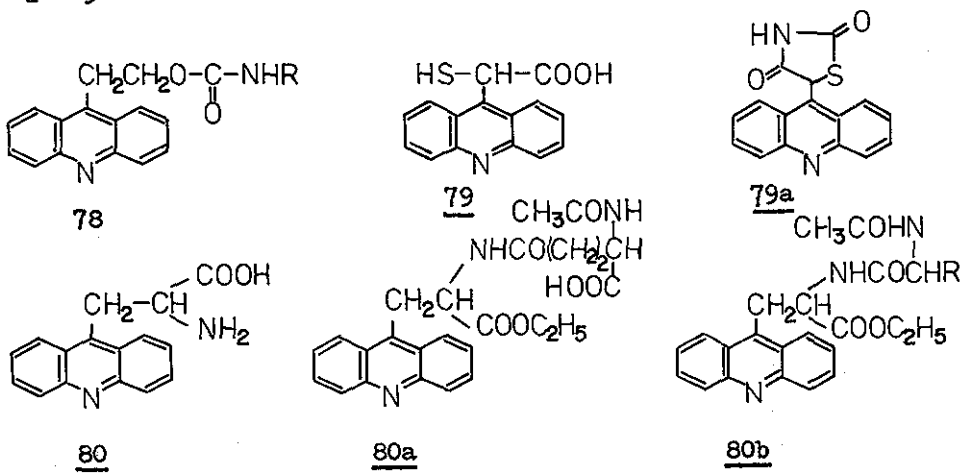
Ivanov[127] has studied complexes of 75 with amines and found two kinds of them: π-complexes and σ-complexes.

Tsuge and Torii have extensively investigated reactions of 9-vinylacridine (75: R=H) with various reagents and isolated a great variety of products, e.g., by the bromination of 9-vinylacridine[128] they have prepared 9-(1,2-dibromoethyl)acridine (76), in order to choose a convenient method to obtain 9-ethynylacridine (77), afforded several products shown on the following page[129]. They have also studied reactions of 9-vinylacridine (75: R=H) with p-substituted nitrosobenzenes[130] and C,N-diarylnitrones[131]; 9-ethynylacridine (77) with nitroso compounds[129], C,N-diarylnitrones[131], amines[132] and active methylene[133] compounds; 1,3-bis(9-acridinyl)propane with N,N-dimethyl-p-nitrosoaniline[134]; 1-(9-acridinyl)-2-benzoylethylene and 9-acridinyl styryl ketone with hydrazines[135].

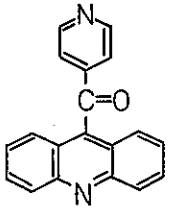


9-Vinylacridine polymer has been obtained from 1,3-bis(9-acridinyl)propane[134] or from 9-vinylacridine[136] and some of its spectral properties were studied[136].

Of other 9-alkylacridines, 2-(9-acridinyl)-ethyl-N-substituted carbamates (78: R=H, C_2H_5, C_6H_5, $SO_2C_6H_4$-p-CH_3) and their 10-hydrochlorides and 10-N-oxides[137] as well as 9-acridinylthioglycolic acid (79) and its derivative (79a) were synthesized. More recently, the peptide derivatives of acridine (80a and 80b: R=C_6H_5, CH_2SCH_3) were prepared from 80 and tested for antitumour activity[139].



It was already mentioned above that α-hydrogen atoms on the alkyl group of 9-alkylacridines were strongly activated by 9-acridinyl moiety. Therefore, the 9-alkylacridines are rather reactive compounds and tens of various derivatives were reported to be prepared from them by reactions with other reactive reagents[140]. For example, if such a methyl group is additionally activated by pyridyl substituent (see compound 62), then it can be oxidized with chromium trioxide in acetic acid to give ketone 81 in 76 % yield or reacts with N,N-dimethyl-p-nitrosoaniline in pyridine giving 82 in 40 % yield which is hydrolyzed in boiling 30 % sulphuric acid to give 75 % of 81[101].



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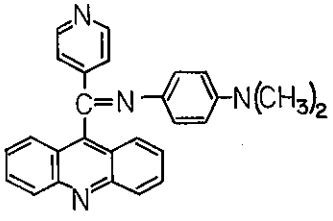

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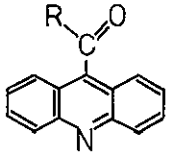


83

9-Methylacridine reacted with N,N-dialkyl-p-nitrosoanilines and when the product of this reaction employing 3-chloroacridine derivative was hydrolyzed, 3-chloro-9-formylacridine was obtained in a high yield[141].

Acridine-9-carboxaldehyde (83: R=H) was also found to be a by-product of the aforementioned conversion of azepine (72) to 9-methylacridine (73)[119] and a rearranged degradation product from carbamazepine-10,11-epoxide[142]. Chemiluminescent reactions of this 9-formylacridine and 9-formyl-10-methylacridinium methyl sulphate as well as two ketones (83: R=C_6H_5, C_6H_4-p-NO_2) were studied and the reaction mechanism has been discussed[143].

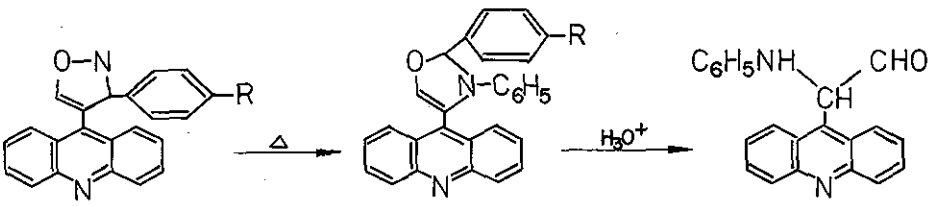
Treatment of the methyl ester (83: R=OCH_3) with hydrazine in refluxing ethanol gave hydrazide (83: R = $NHNH_2$)[144]. Other

hydrazides (83: R=$N(CH_3)=CHCH_3$, $NHN(CH_2)_5$, $N(CH_3)NHCH_3$, $N(CH_3)NH_2$) and hydrazone derivatives of 9-formylacridine were also synthesized and a study of the chemiluminescent reaction products under various conditions was carried out[144].

Of other acridine derivatives of structure 83, the following amides were synthesized. 1,2,3,4-Tetrahydroacridinecarboxamides (83: R=$N(C_2H_5)_2$, $N(CH_2CH_2OH)_2$, morpholino) were prepared by reaction of the acid chloride (83: R=Cl) with the appropriate amines[145]. On the other hand, Italian workers[146] have reported direct and selective amidation of heterocyclic compounds including acridine amido radicals. These radicals were obtained by oxidation of formamide, N-alkylformamide and N-alkylacetamide with various oxidizing agents. Acridine-9-carboxamide (83) was prepared in high yield in this manner[146].

Cârje[147] has reported syntheses of esters and thioesters of 1,2,3,4-tetrahydroacridine-9-carboxylic acid and its 7-chloro and 7-methoxy derivatives. Thus, derivatives of 83 (R=$SCH_2CH_2N(C_2H_5)_2$, OCH_2CH_3, OCH_2CH_2OH, OCH_2CH_2Cl) were obtained from the acid chloride (83: R=Cl) and 2-diethylaminothioethanol, ethanol, glycol, and ethylene chlorohydrin, respectively. The IR spectra of these products were also discussed[147].

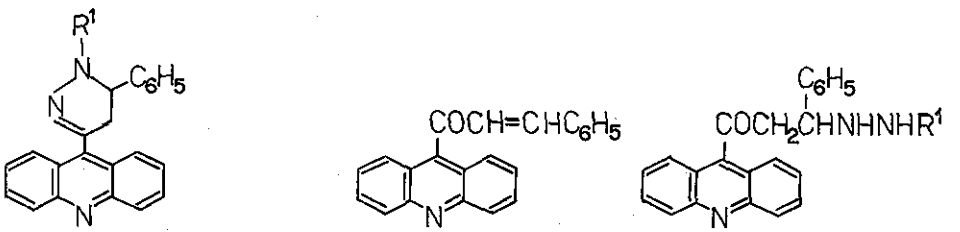
During last years several compounds of the previously known structure, but now obtained in a somewhat another way, were reported. Tsuge and Torii[130] have synthesized acridine-9-carboxaldehyde-N-(p-N,N-dimethylaminophenyl)anil from 1-(9-acridinyl)-2-methylethylene and p-nitroso-N,N-dimethylaniline and discussed the mechanism of the product formation and its reactions. These authors have also studied the reaction of 9-vinylacridine and 9-ethynylacridine with C,N-diphenylnitrone. In the latter case, the corresponding



84 85 86

4-isoxazoline compound (84) was found as a product, which was converted by thermal rearrangement into 4-oxazoline (85), and this was hydrolized to give 9-acridinylanilinoacetaldehyde (86)[131].

The derivative of 75 (R=COC_6H_5) reacted with R^1NHNH_2 (R^1=C_6H_5, H, p-Cl- and p-CH_3-C_6H_4) at room temperature to give mainly pyrazoline derivatives (87)[135]. Compound 88 with R^1NHNH_2 at room temperature gave Michael type adduct (89) as the major product[135].



87 88 89

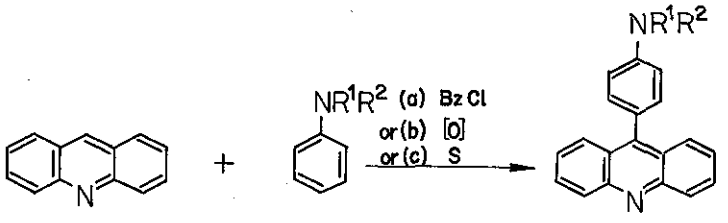
Of other acridine derivatives containing C^9-C bond, 9-cyanoacridine is most important. This compound has been known for a long time. Recently, Happ and Janzen have studied the mechanism of reaction of cyanide ion with acridine and found that this reaction proceeded *via* reversible addition of cyanide ion to acridine to yield the 9-cyanoacridanyl radical which was then converted to 9-cyanoacridine by the action of the oxidizing agent. A similar addition of cyanide ion to aromatic hydrocarbons, e.g., anthracene, has also been proposed[149,150]. Oxidative cyanation of acridine N-oxide was studied, too[151].

Some cyanoalkyl derivatives of acridine will be considered in Chapter concerning derivatives of acridans.

5. 9-Arylacridines

So far comparatively lettle attention has been attracted by the 9-arylacridines and a huge number of papers published in last years is rather surprising. Although the majority of physico-chemical properties of the 9-phenylacridine derivatives remains unexplained, a considerable progress is noticeable in this area.

Of the 9-arylacridine derivatives, 9-aminophenylacridines (90) are most frequently reported to be prepared. Their synthesis is achieved in a few chief manners. Thus, acridines react with dialkylanilines under nitrogen in the presence of benzoyl chloride as an acylating agent in DMF[152-155] or other organic solvents[105,106] yielding 90 (route a).

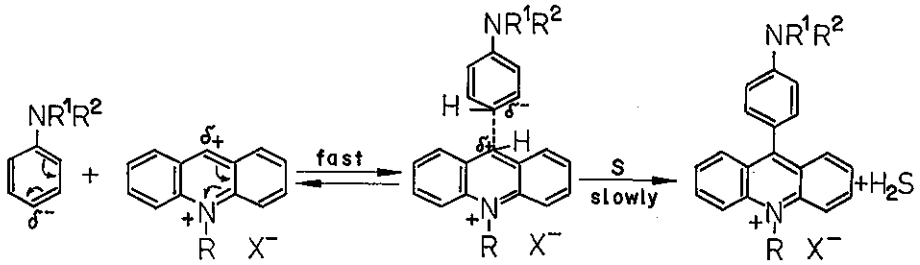


90

Pure quaternary and protonic salts of 9-aminoarylacridines (90), used as intermediates in the syntheses od dyes and physiologically active compounds, can be prepared by treating the quaternary or protonic salts of acridine with arylamines in a polar solvent while mixing the reaction mixture by bubbling air[156] (route b). When acridine methiodide is employed, however, the unexpected phenylacridinium triiodides are obtained[157,158].

The 9-aminoarylacridines (90) and their salts are also prepared by treating acridinium salts with the appropriate aromatic amine in the presence of sulphur[159-163] (route c). The reaction is inhibited by electron-withdrawing groups in both *para* and

ortho positions in the aniline nucleus[161]. The mechanism of this condensation reaction was studied[164,165] and it was found that the reaction of acridinium salt with aniline in the presence of sulphur involved a fast formation of weak complex (91) followed by slow dehydrogenation with sulphur to give 92.

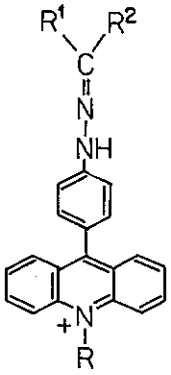


91 92

9-Substituted acridines do not form such complexes as 91 and sulphur does not react with acridinium methiodide. The highest yield, independent on radical inhibitors of 92, was observed in polar solvents. With increasing of positive charge on C^9 the yield of 92 increased. Moreover, no ESR signals could be observed in the samles of the reaction mixture. These findings support the ionic mechanism of the reaction under consideration[165].

Chupakhin et al.[166,167] have prepared acridinium phenylhydrazone derivatives (93: R=R^1=H, CH_3; R^2=C_6H_5, p-Cl-, p-Br-, p-I-, p-OCH_3-C_6H_4, and others) from acridinium salts and phenylhydrazones under oxidizing conditions. The reaction proceeded in liquid sulphur but better yields were obtained with bubbling air through the reaction mixture.

9-(4-Hydroxyaryl)acridinium salts (94) have been synthesized[168] by reaction of quaternary or protonic acridinium salts with phenols. The reaction was performed in liquid sulphur at



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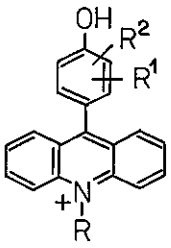

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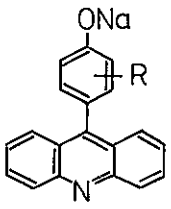


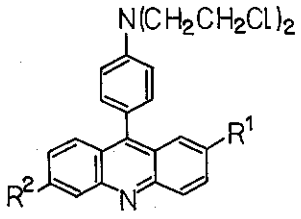
95

high temperature in DMF in the presence of air or in an inert solvent in the absence of air. In the latter case, acridinium cation acted as an oxidizing agent for the activated complex composed of second acridinium moiety and phenol. Therefore, acridan is a major by-product in this reaction. A series of di- and triphenols, amino- and methoxyphenols and ethyl esters of polyphenols has been prepared in this manner.

Phenolates appeared to be even better nucleophiles than phenols themselves in the substitution reactions of hydrogen atom at C^9 of the acridine ring[169]. The reaction proceeded with free base of acridine in DMF sparged with air. When such substituents as CH_3, NH_2, OH or OCH_3 are present in *meta* position in the phenolate, the products 95 are obtained in higher yields.

Acridine was also found to undergo condensation reactions with other aromatic and heteroaromatic compounds in the presence of an acylating agent, largely benzoyl chloride, in an organic solvent, e.g., benzene, DMF, etc. Following this route, acridine was condensed with cyclopentadiene, indene and azulene[170], 1,2,3,4-tetrahydrochinoline[105,153,171], indole[105,106,163,172,173], pyrrole[129,174-176], furan[177] and pyrazolone[178]. The acylating agent may be replaced by aluminium and mercuric salts[172].

All the preceding methods of syntheses of the acridine derivatives containing an aryl substituent in 9 position involve condensation of various reagents with unsubstituted acridine at the 9 position[152-178]. A few other papers describe successful substitution of halogen atoms in 9-halogenoacridine by aryl groups. Thus, 9-chloroacridine[179] was arylated in phosphoryl chloride to give 96 (R^1=H, OCH_3, OC_2H_5; R^2=H, NO_2, Cl), 9-bromoacridine[180,181] reacted with p-halostyrene to yield 9-p-vinylphenylacridine (97) and its polymers[181], and condensation of



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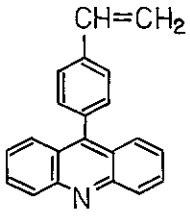

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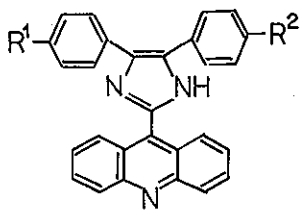
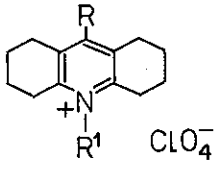


98

acridine-9-carboxaldehyde[182,183] with p-R^1-$C_6H_4COCOC_6H_4$-p-R^2 in acetic acid containing ammonium acetate gave 98 (R^1=H, OCH_3, Br; R^2=Br, OCH_3, NO_2). Some of compounds 96 exhibited pharmacological activity against moose sarcoma and had low toxicity[179].

A series of 9-aryl-1,2,3,4,5,6,7,8-octahydroacridines and their perchlorates (99) with the following substituents in 9 position has been prepared: phenyl[184], p-nitro- and p-methoxyphenyl[185], 2-furyl[186], 3- and 4-pyridyl[187].



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The last step in all the preceding syntheses involves oxidation of the cyclization product of the appropriate ketones with ammonia or aniline or other compounds containing the amino group. The mechanism of such a condensation is discussed[184].

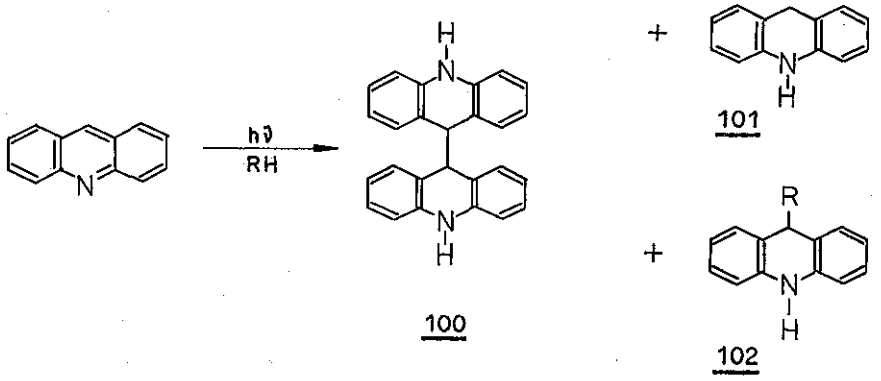
Among other numerous syntheses of various derivatives of 9-arylacridine, it is worth to mention the condensation of 2-arylidene-3,4-dihydro-1(2H)-naphthalenone with either -tetralone in the presence of ammonium acetate affording 9-aryl-3:4,5:6-dibenzo-1,2,7,8-tetrahydroacridine or cyclohexanone yielding 9-aryl-3:4-benzo-1,2,5,6,7,8-hexahydroacridine[188], and the conversion of o-anilinoketimines to 9-phenylacridine or its derivatives[189].

In summary, the 9-arylacridines can be prepared from acridine itself[152-178], from 9-substituted acridines[179-183] and from non-acridines[184-189]. The mass spectra of 9-phenylacridine derivatives[190] and 9-aminophenylacridine derivatives[191] were determined and fragmentation patterns discussed.

6. Acridans

Acridans may be prepared according to the methods considered by Selby[192]. This author gave a detailed description of all the techniques which were of preparative value and, therefore, I am not going to dwell upon this subject. Here, particular types of sources of acridans and types of substituents in 9 position of 9,10-dihydroacridine will be considered.

Acridine itself can be converted to the acridan derivatives in numerous manners. Among them, the photoreduction of acridines has been developed extensively in last years by several groups of investigators. In general, the distribution of products depends upon the nature of the solvent used but the following compounds are usually synthesized by a photolysis in protic solvents:



Irradiation of acridine has been investigated in the presence of various alcohols[193-201], nonpolar organic solvents such as cyclohexane, toluene, etc.[202], in mixtures of alcohols and nonpolar solvents[203] and its reaction mechanisms proceeding under particular conditions widely discussed throughout these reports. The acridanyl radical, formed by initial hydrogen-atom abstraction,

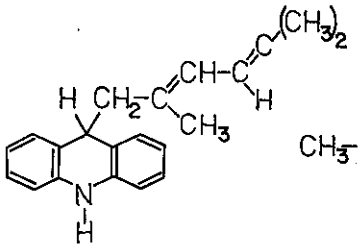
has been identified as the key intermediate in the reaction, though there is a certain evidence that a "molecular mechanism" (involving formation of acridan by a process in which the acridanyl radical cannot be detected) may account for a small portion of the reaction. On the basis of kinetic investigations it is suggested that the primary reactive state of acridine towards most hydrogen donors is a low singlet excited state[198]. Similar studies on the irradiation mechanism were carried out with 9-methylacridine[204], 9-phenylacridine[205-207], acridine N-oxide[208] and 9-cyano- and 9-chloroacridine N-oxides[209].

The photoreduction of acridines with various aliphatic carboxylic acids results in decarboxylation and formation of 9-alkylacridans (102) in good to excellent yields together with small amounts of biacridan by-products (100)[210-212]. A good yield of compounds 102 and 9-alkylacridine (57) is also observed when acridine is photoreduced in the presence of trialkylboranes[100].

Under the irradiation conditions normally employed for the photoreduction, benzophenone as well as benzylideneacetophenone and benzylideneacetone were found to be photoreduced by acridan (101) and in each case 1:1 adducts (100) were isolated[213].

More recently, two examples showing the application of photochemically allowed $[4\pi + 2\pi]$ cycloaddition of acridine with cyclohexadiene[214] and quadricyclane[215] have been reported. However, compound 103 was isolated as a major product in the photoreduction reaction of acridine with 2,5-dimethyl-2,4-hexadiene[214].

Acridine was found to undergo the Chichibabin reaction in dimethylaniline in the presence of sodium amide and 9-aminoacridine and biacridans (100) were chief products identified[216].



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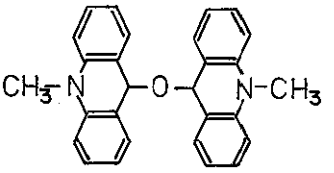

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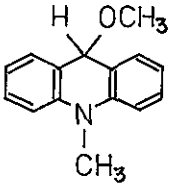


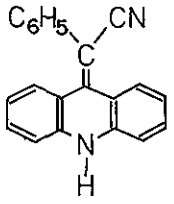
105

Heating acridine and phenylhydrazine in DMF at 130° for 5 hr yielded 9,9'-biacridan (100) in 72 % yield[217]. Similarly, 73 % yield of N,N'-dimethyl-9,9'-biacridan was obtained by treating N-methylacridinium iodide with phenylhydrazine[217]. On the other hand, N-methylacridinium iodide was converted to bis(9,10-dihydro-10-methylacridinyl-9)ether (104) in aqueous solution of sodium hydroxide whereas when it was treated with methanolic sodium hydroxide then only compound 105 was formed[218].

It was previously reported[219] that very active methylene compounds and sodio ketones underwent noncatalytic 9,10-addition to acridine to give derivatives of acridan 102. Recently, Levine and Sheppard[220] have extended this type of reaction to the synthesis of α-(9-acridanyl)phenylacetonitrile (106).

The nucleophilic alkylation of acridine ring has been attained by the action of sulphonylcarbanions[99,221] and anionized Schiff bases[222] affording acridans of general formula 102. It is worth to note that pyridine, quinoline and isoquinoline did not react with those anions under the same conditions[99,220-222]. On the other hand, both quinoline and acridine reacted with benzyl iodide in the presence of concentrated sulphuric acid and iron[223]. In the case of acridine, 9-benzylacridan and 9,10-dibenzylacridan were obtained[223].

The reductive silylation of acridine by treatment with a lithium dispersion and $(CH_3)_3SiCl$ gave 107 $R=R^1=Si(CH_3)_3$, selective acetylation of which gave 107 (R,R^1 given: $H,COCH_3$; $Si(CH_3)_3,H$; $Si(CH_3)_3,COCH_3$)[224].



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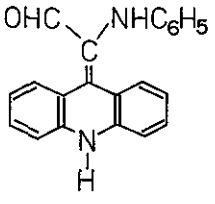
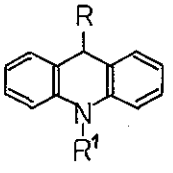


106a



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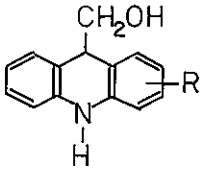


108

A series of dialkyl 9,10-dihydro-9-phosphonates (107: R= $PO(OAlkyl)_2$, R^1=H) was obtained in a good yield by reaction of acridine hydrobromide[225] or N-methylacridinium methosulphate[226] with $(AlkO)_2PONa$ or acridine itself with $ClP(OAlk)_2$ in alcohol[227-229].

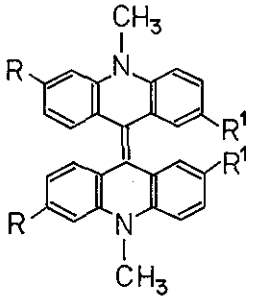
Finally, 2-chloroacridine reacted with Grignard reagent $[(CH_3)_2N(CH_2)_3MgCl]$ in refluxing THF to give 9-aminopropylacridan[87]. Similarly, the Grignard reagent from 1-iodo-11-methoxyundecane reacted with acridine in refluxing ether giving 9-(11-methoxyundecyl)acridan[61].

All the syntheses of the acridan derivatives described above were achieved starting from acridine or its derivatives excluding 9-substituted compounds[61,87,99,193-229]. Methods employing 9-substituted acridines will be considered below.

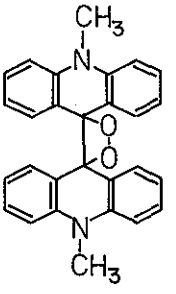
The hydrolysis of 9-acridinylanilinoacetaldehyde (86) with 20 % aqueous hydrochloric acid at room temperature afforded 106a in a good yield[131]. On the basis of the chemical conversion and spectral data, 106a was assigned to be (9,10-dihydro-9-acridinylidene)anilinoacetaldehyde[131].

A series of acridanemethanols (108) was prepared by reducing 9-acridine carboxylic acids[230] and acridine-9-carboxaldehyde[231].

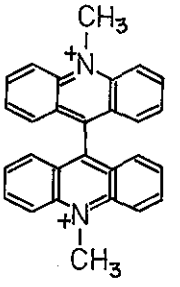
Irradiation of 10,10'-dimethyl-9,9'-biacridylidene (109a: R=R^1=H) in solvents saturated with oxygen in the presence of zinc tetraphenylporphine leads to the corresponding 1,2-dioxetane (109b)[232]. Compound 109b has also been proposed as an intermediate in the chemiluminescence reactions of lucigenin (109c)[233].



109a



109b

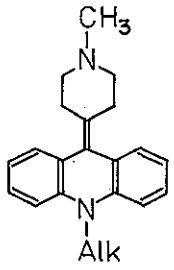


109c

The study of the mechanism of uncatalyzed thermal Z,E isomerization in the biacridan series (109a: R=Cl, R^1=OCH_3) was carried out and the remarkably low barriers associated with this isomerization were found[234].

The addition of 9-acridanones to the Grignard reagent derived from 4-chloro-1-methylpiperidine afforded the piperidylidene derivatives of acridan (110)[235]. Several of these compounds having an appropriate substituent, e.g., R=CF_3, Cl, SCH_3 in the 2 position, were potent neuroleptic agents[235].

The reaction of some N-alkylacridinium cations with methoxide ion has been investigated by Bunting and Meathrel[236,237]. The kinetics of the formation and decomposition of the pseudo-bases (111) have been studied and possible mechanisms for the reaction are discussed on the basis of the observed activation parameters and isotope effects of related reaction[236-238].



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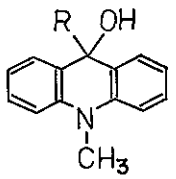

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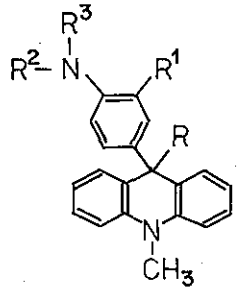


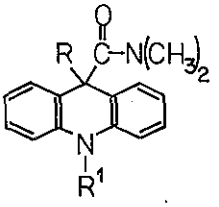
112

It was already mentioned that reaction of acridinium salts with hydrazines resulted in the formation of 9,9'-biacridan (100)[217]. If 9-amino-10-methylphenylacridinium iodide is employed then 9-aminophenyl-9-hydrazino-10-methylacridan (112: R=$NHNH_2$, R^2=R^3=H) is formed[239,240] whereas 10-methyl-9-phenylacridinium iodide under these conditions yielded 1,2-bis(9,10-dihydro-10-methyl-9-phenyl-9-acridinyl)hydrazine[240].

9-(Monoalkylaminophenyl)acridinium salts easily reacted with formic acid in the presence of triethylamine to yield 9-formylaminoarylacridan (112: R = R^1 = H, R^2=CHO, R^3=alkyl)[241]. The formamide group was subsequently hydrolyzed in boiling alcoholic solution of sodium hydroxide and acridan 112 (R=R^1=R^2=H, R^3=alkyl) was isolated as a final product. The N,N-dialkyl derivatives of 9-aminophenylacridinium salts were decomposed under these conditions and unsubstituted acridine or N-methylacridine as well as dialkylanilines were isolated[241].

In the course of the synthesis of 9,10-disubstituted dihydroacridines of possible pharmacologic interest, Digenis[242] has reported an unusual benzyl group migration from 10 to 9 position when 10-benzyl-9-methylacridan was treated with n-butyl lithium in THF at room temperature. NMR and deuterium oxide-exchange

studies[243] suggested that the rearrangement occurred intramolecularly. Several other acridan derivatives (113: R=H, CH_3, $CH_2C_6H_5$; R^1=H, CH_3, $CH_2C_6H_5$) were synthesized from N,N-dimethyl-9-carboxamidoacridine (83: R=$N(CH_3)_2$) and their NMR spectra studied in order to investigate the conformational influences of methyl and benzyl substituents[244].



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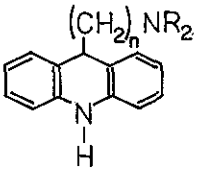

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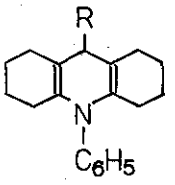


115

9-Aminomethylacridan (114: n=1, R=H) and N,N-dimethyl-9-aminomethylacridan (114: n=1, R=CH_3) were treated with sodium 1,2-naphthoquinone-4-sulphate and nitrous acid[245]. Cleavage of the aminomethyl side chain during oxidation to produce acridine was observed with the former compound but not with the latter one. A mechanism based on electrophilic attack at the primary amine nitrogen of the side chain was proposed for the oxidation of 9-aminomethylacridan (114: n=1, R=H) and similar compounds[245].

More recently, the similar oxidation of the acridan derivative (114: n=3, R=CH_3) has been achieved by anaerobic irradiation with visible light resulted in the quantitative conversion of this acridan to its acridine derivative[246]. The anaerobic photodecomposition was catalyzed by the monosodium salt of riboflavin 5-phosphate[246].

Oxidations of analogues of dihydropyridines and related compounds are of interest as models for biological oxidation-reduction reactions. Various oxidizing agents have been used

including N-methylacridinium ion[247] and trifluoroacetophenone[248]. Recently, kinetic isotope effects have been measured in the reaction of N-methylacridan with a series of strong (and hydride) acceptors: 1,4-benzoquinone, 2,3-dicyano-1,4-benzoquinone, chloranil, and tetracyanoquinodimethane[249].

More recently, the electrochemical oxidation of acridan derivatives (107: R=CH_3, C_6H_5, C_6H_4-p-$N(CH_3)_2$; R^1=CH_3) has been reported[250]. The reduction involves sequential loss of two electrones to give the corresponding derivatives of 74a[250].

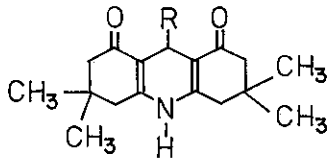
There are also a few reports of synthese of the acridan[115] and 1,2,3,4,5,6,7,8,9,10-decahydroacridine (115)[118, 251, 252] derivatives achieved by the condensation of the appropriate ketones with aniline or its derivatives.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethylacridan-1,8(2H,5H)-dione-9-carboxylic acid (116: R=COOH) was also synthesized and converted into a complex series of products by pyrolysis[253]. One of the primary products was the decarboxylation product (116: R=H).

More recently, Inayama and Mamoto[254] have prepared a series of p-hydroxyphenyldecahydroacridinediones (116a: R=alkyl, phenyl, carboxyalkyl; R^1=H, $CH_2C_6H_5$, alkylsulphonyl; R^2=H, OCH_3) by reaction of p-hydroxyphenyldi(dimedonyl)methanes or their derivatives, e.g., anhydrides, with amines (RNH_2). Some of these products have anticonvulsant, antidepressant, antibacterial and antitumour activity[254].

Of other acridan derivatives, a series of compounds 117 (X=H, OCH_3, Br; Y=H, CH_3, OCH_3, NO_2) was prepared by reaction of 9,10-dimethylacridinium salts with aromatic o-hydroxyalde-

hydes[255]. Several acridan bispyrrolinyl derivatives (118) were obtained by treating 9,9-dimethylacridan with 2-pyrrolidinones in the presence of phosphoryl chloride[256]. Four derivatives of 119 (R=H, CH_3; R^1=Cl, CH_3) have also been prepared and their ^{11}B and ^1H NMR studies carried out[257].



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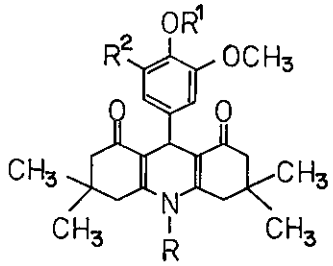

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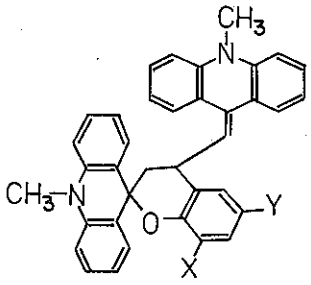

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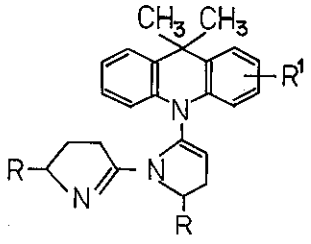

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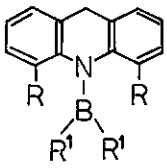
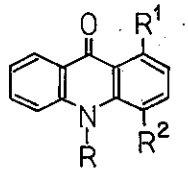


119

7. 9-Acridanones

The preparation and properties of substituted 9-acridanones have been reviewed in details by Gagan[258]. Unexpectedly, there have been only a few reports of syntheses of these compounds in last six years.

9-Acridanones were traditionally produced by the cyclization of the appropriate diphenylamine-2-carboxylic acids using such cyclization agents as sulphuric acid[259] or polyphosphoric acid[260,261]. Following this procedure, compounds 120 (R^1=H, NO_2; R^2=NO_2, CH_3; R^3=$(CH_2)_{2-3}N(CH_3)_2$)[259], 121 (R = NO_2; R^1=R^3=R^4=H; R^2=s-butyl)[61], 121 (R=H, NO_2; R^1,R^2,R^3,R^4=H,OCH_3,OC_2H_5)[260,261], 122 (R=R^1=R^2=H)[262] and 122 (R=H; R^1=H, CH_3; R^2=H, 6-CH_3, 6-Cl, 6,7-$(CH_3)_2$, 8-OCH_3)[263] were obtained in good yields. Some of compounds 120 exhibited antitumour activity in some tests used[259].



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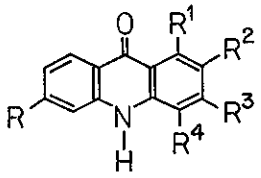

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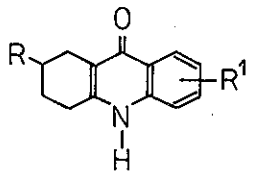
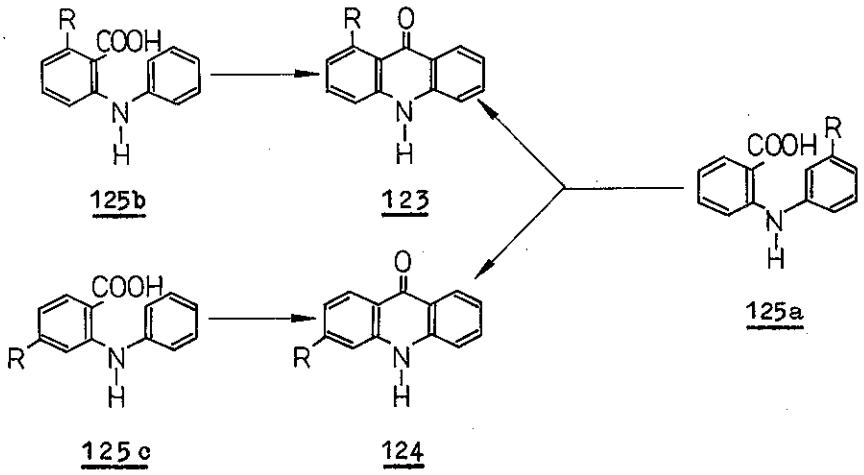


122

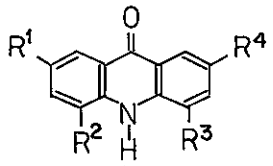
If 1- or 3-substituted 9-acridanones (123 and 124) are required then the cyclization of the appropriate 3 -substituted diphenylamine-2-carboxylic acids (125a) is carried out and this leads to a mixture of the isomeric compounds. The separation of such a mixture may be accomplished but always it results in considerable loses of the products. Nevertheless, this route is sometimes followed if it appears to be the only method to get some particular derivatives, e.g., a number of attempts were made to prepare 125b (R = Br) but all were unsuccessful[264]. In such cases the separation of 123 and 124 must be undertaken.



A very similar method of the 9-acridanone synthesis to that described above involves a two-step procedure with 9-halogeno-acridines being intermediates. These are heated with aqueous mineral acids and in this way hydrolyzed to the corresponding 9-acridanones. A series of alkyl-substituted 9-acridanones has been synthesized according to this manner[265]. Other 9-substituted acridines, e.g., 9-amino-, 9-alkyl- and 9-arylamino-, 9-alkoxy- or 9-azidoacridines, undergo hydrolysis in the similar manner giving 9-acridanones as products. Of the latest reports, it is worth to mention that acridine derivatives containing an active methyl group in the 9 position (e.g., compound 58) can be converted to 9-acridanone in 80 % yield by treatment with boiling 10 % sulphuric acid[112].

The oxidation of acridine hydrochloride with quaternary salts (alkyl iodides and heterocyclic compounds) to give 9-acridanone was also studied[101-103]. The reaction was found to be of second overall order and of first oredr with respect to each reagent. The mechanism, which involves intermediates such as 9-alkylacridans and 9-alkylacridines, was discussed[103].

Rindone and Scolastico[266] have reported the oxidation of acridine with cerium(IV) ammonium nitrate in methanol to yield 9-acridanone (66 %) and small amounts (less than 5 %) of nitration products (126: R^1,R^2,R^3,R^4=H, NO_2) and biacridanone (127). The mechanism of the 9-acridanone formation and its nitration is discussed as well[266].



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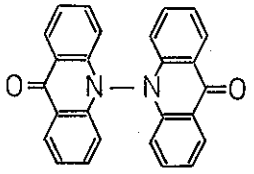


127

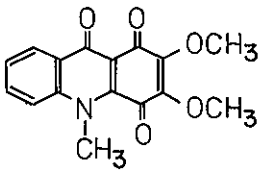
Similarly, treatment of acridine with potassium hydroxide at 300-350° gave 9-acridanone in 28 % yield[216].

9-Chloroacridine was also converted to 9-acridanone in satisfactory yields in the course of the reaction with carboxylic acids[267]. Acyl chlorides were other products when the reaction was performed in benzene. In the presence of alcohols, the carboxylic acids were converted to the corresponding esters. The mechanism of these reactions was suggested[267].

The greater part of the 9-acridanone derivatives was prepared from other easily available 9-acridanones or acridines. Numerous examples of such a procedure followed recently might be mentioned[39,264,265,268-276]. Prager et al.[264,268-272] extensively studied nucleophilic substitution in the 9-acridanone series. Thus, the 1- and 3-bromo-10-methylacridanones were cleanly converted by sodium methoxide in dimethyl sulphoxide into the respective methoxy compounds. On the other hand, the 2- and 4-bromo isomers in the same solvent and 1-, 2-, 3-, and 4-bromo-10-methylacridanones underwent a radical chain reduction to 10-methylacridanone[262].

Reaction of the isomeric bromo-10-methylacridanones with potassium amide, lithium piperidine and piperidine was also studied and the distribution of products discussed in terms of the addition-elimination and elimination-addition mechanisms[268].

More recently, they have studied the reaction of polyalkoxy-10-methylacridanones with sodium methoxide in methanol and dimethyl sulphoxide[270], the kinetics of this reaction[271] and another one involving 2,3-dimethoxy-10-methyl-9-oxoacridine-1,4-quinone (128) and sodium hydroxide[272]. The mechanisms suggested were widely discussed throughout these papers.



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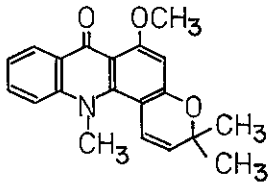

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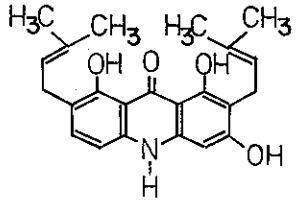


130

The synthesis of compounds related to acronycine (129), an acridanone alkaloid, has been reported[273]. These analogues were tested for anticancer, antiviral, antibacterial, antiprotozoal and anthelmintic activity *in vivo*. None of the derivatives and analogues prepared showed enhanced activity in the tests used.

Chatterjee and Ganguly[274] have isolated from *A. monophylla* a new 9-acridanone alkaloid, atalaphyllidine. Its structure (130) was derived from spectroscopic studies and chemical reactions.

Of other reports on the 9-acridanone alkaloids, two review articles are available[275,276].

A series of amino derivatives of 1-nitro-9-acridanone has also been synthesized as intermediates for potentially anticancer preparations[277]. Of other biologically active 9-acridanones, 10-carboxymethylacridanone was tested for antiviral activity[278].

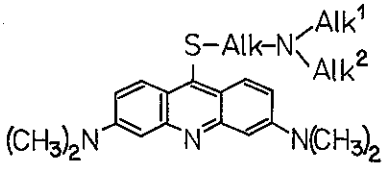
Of other syntheses of the 9-acridanone derivatives, 2-halobenz b acridine-6,11,12-triones (2-Cl, 2-Br, 2-I) were prepared by treating 1,4-naphthoquinone with 5-haloanthranilic acids and cyclizing with a mixture of sulphuric acid and acetic acid[279], diaminobibenzyl derivatives were condensed with 1-chloro-4-nitro-9-acridanone to give linear diacridanones[280] as well as octafluoro-9-acridanone was obtained by diazotisation of tetrafluoroanthranilic acid[281] and by electrochemical oxidation of 2-aminononafluorobenzophenone[282]. Moreover, Postescu and Suciu[283] have proposed a suitable method for the N-alkylation of 9-acridanone by using DMF as solvent. A number of new derivatives as well as previously reported, but now synthesized in a different manner, have been obtained. The reaction pathway consists in the formation of the potassium salt of 9-acridanone in DMF which was then allowed to react in the same reaction medium with an alkylating agent to produce the corresponding N-alkyl-9-acridanone[283].

Spectral studies of 9-acridanones have focused a good deal of attention in last years. Acheson and Bolton[265] have prepared a series of alkyl-substituted 9-acridanones and 9-chloroacridines for NMR, IR and UV studies. Prager[284] has employed NMR spectroscopy and chemical methods for the structural investigations of hexabromo-9-acridanone. Ionescu and co-workers[285-290] have extensively studied NMR, UV and IR spectra of various substituted 9-acridanones.

8. Other 9-substituted acridines

Of other 9-substituted acridines, 9-halogen derivatives are of first rank. These compounds are most frequently used as intermediates in preparation almost all the other 9-substituted acridines, especially 9-aminoacridines and 9-acridanones, owing to the high reactivity of the halogen atom (most frequently chlorine or occasionally bromine) in this position. Therefore, the syntheses of these compounds are described in publications concerning final products and only syntheses of 9-bromoacridine[291], perchloroacridine[292], and 9-chloroacridinium 2-chloro-1-(chlorosulphinyl)-2-oxoethylide[293] are reported separately.

Second most widely synthesized acridine derivatives were those containing the sulphur atom bonded to C^9. A series of 3,6-bis(dimethylamino)-9-dialkylaminoalkylthioacridines (131) was synthesized in 10-94 % yield by the condensation of 3,6-bis(dimethylamino)-9-acridanthione (132) with the appropriate dialkylaminoalkyl halide in DMF[76]. Various ways of syntheses



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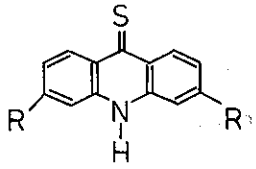

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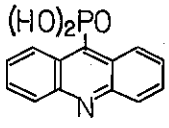

133

of compounds 131 and 132 were outlined and compound 132 appeared to be a very useful intermediate. Some of compounds 131 revealed various biological activities in *in vitro* and *in vivo* tests used[76].

The rearrangement of acridine N-oxides in acetyl sulphide to give 9-thioacridanone (132) was also reported[294]. The mechanism of this reaction was discussed on the basis of kinetic data[294].

Ionescu et al. have extensively studied properties of thioacridanone by means of UV[295], IR[296] and NMR[297] spectroscopies and correlated the data with those of 9-acridanone. They have also prepared 1,2,3-trimethoxy-9-thioacridanone N-oxide[88], 9-methylthioacridine N-oxide[298] and other 9-substituted acridines as well as their N-oxides and widely discussed their UV spectra[298].

The Soviet authors[299] have also reported UV and IR spectra of 9-thioacridanone, N-methylthioacridanone and 9-methylthioacridine and discussed the tautomeric equilibrium occurring in neutral solutions.

More recently, reactions of some 9-alkylaminoacridine derivatives which are of pharmacological interest (viz. C-283 or Ledakrin (27) and m-AMSA (30), cf. section 3) with thioles have been investigated[300,301]. Nucleophilic attack at the acridine C^9 position by thiols was found to be of greatest biological relevance since such functional groups are normally encountered in enzyme proteins[300]. The relationship among substituents in both acridine nucleus and the 9-amino side chains, thiolysis rates, and biological activity of substituted acridines have been discussed[300,301].

Redmore[225-227] and Sheinkman[228,229,302,303] have provided two approaches to the preparation and study of 9-acridinephosphonic acid (133) and its esters. These compounds have many uses, e.g., as bacteriocides, herbicides, corrosion inhibitors,

chelating agents, etc. The mechanism of the synthesis was discussed taking into account various reagents used[155].

To end with, it is worth to mention kinetic investigation of photochemical protonation of acridine in nonaqueous solutions[286], electron-donor-acceptor properties of acridine and its conjugated acid and related compounds[305], reaction of acridinium thiocyanate with zinc complexes[306,307] and syntheses of 1,2,3,4,5,6,7,8-octahydroacridinium chlorides[308] and perchlorates[308,309].

9. References

1. A.Albert, "Drug Design", vol. 3, Academic Press, Inc., New York 1972, p. 229.
2. A.Albert, Brit. J. Exp. Pathol. 1942, 23, 69.
3. L.S.Goodman and A.Gilman, "The Pharmacological Basis of Therapeutics", 4th ed., Macmillan, New York 1971, pp. 1080, 1095.
4. A.Chandler and C.Read, "Introduction to Parasitology", 10th ed., Wiley, New York 1967, p. 187.
5. A.Albert, "The Acridines", 2nd ed., E.Arnold Ltd., London 1966, p. 431.
6. A.Ledóchowski, VII Intern. Congress of Chemotherapy, vol. 2, Prague 1972, p. 133.
7. B.F.Cain and G.J.Atwell, Europ. J. Cancer 1974, 10(8), 539.
8. A.Bernthsen, Justus Liebigs Ann. Chem. 1878, 192, 1; see also Ref. 9, p. 67; Ref. 10, p. 19; Ref. 11, p. 23.
9. A.Albert, "The Acridines", 1st ed., E.Arnold Ltd., London 1951.
10. R.M.Acheson, "Acridines", 1st ed., Interscience Publishers Ltd., London 1956.
11. R.M.Acheson, "Acridines", 2nd ed., Wiley, New York 1973.
12. G.Löber, Z. Chem. 1971, 11(3-4), pp. 92, 135.
13. S.Johne and D.Gröger, Pharm. 1972, 27(4), 195.
14. J.Reisch, K.Szendrei, E.Minker and I.Novák, Pharm. 1972, 27(4), 208.
15. N.R.Raulins, Ref. 10, p. 13.
16. H.Graboyes, E.L.Anderson, S.H.Levinson and T.M.Resnick, J. Heterocycl. Chem. 1975, 12(6), 1225.
17. A.Albert, J. Chem. Soc. 1948, 1225.
18. T.D.Tuong and M.Hida, Bull.Chem.Soc.Japan 1970, 43(6), 1763.
19. Idem, Bull. Chem. Soc. Japan 1971, 44(3), 765.

20. Idem, J. Chem. Soc., Perkin Trans. II 1974(6), 676.

21. B.F.Cain, R.N.Seelye and G.J.Atwell, J. Med. Chem. 1974, 17(9), 922.

22. B.F.Cain, G.J.Atwell and W.A.Denny, J. Med. Chem. 1975, 18(11), 1110.

23. B.F.Cain and G.J.Atwell, J. Med. Chem. 1976, 19(9), 1124.

24. Idem, J. Med. Chem. 1976, 19(12), 1409.

25. J.W.Schulenberg and S.Archer, Org. React. 1965, 14, 1.

26. A.Ledóchowski, W.Gruszecki, B.Stefańska and B.Horowska, Polish Pat. 60,794.

27. Idem, Polish Pat. 64,147.

28. B.Wysocka-Skrzela, This University, personal information.

29. B.Adcock, Ref. 11, p. 109.

30. B.F.Cain, G.J.Atwell and R.N.Seelye, J. Med. Chem. 1971, 14(4), 311.

31. B.F.Cain, G.J.Atwell and W.A.Denny, J. Med. Chem. 1976, 19(6), 772.

32. G.J.Atwell, B.F.Cain and R.N.Seelye, J. Med. Chem. 1972, 15(6), 611.

33. A.Ledóchowski, M.Bogucka, B.Stefańska, B.Horowska, J.Zieliński and C.Radzikowski, Polish Pat. 60,640.

34. A.Ledóchowski and J.Zieliński, Polish Pat. 66,639.

35. B.Horowska and A.Ledóchowski, Roczniki Chem. 1971, 45(7-8), 1447.

36. B.Stefańska and A.Ledóchowski, Roczniki Chem. 1972, 46(9), 1637.

37. A.Ledóchowski, J.Zieliński, A.Głowacki, J.Maruszewski, A.Irzyłowska and K.Stepnowska, Roczniki Chem. 1976, 50(2), 341.

38. R.Osman, D.Gertner, A.Shenhar and A.Zilkha, Isr. J. Chem. 1972, 10(4), 799.

39. W.Müller, H.Gaedtke and P.Conradt, Justus Liebigs Ann.Chem. 1973, 933.

40. J.K.H.Ma, P.-L.Hsu and L.A.Luzzi, J. Pharm. Sci. 1974, 63(1), 32.

41. A.K.Sukhomlinov, A.N.Gaidukevich, A.I.Goncharov and I.Yu.Kholupyak, Khim.-Farm.Zh. 1971, 5(2), 31.

42. A.N.Gaidukevich, A.K.Sukhomlinov, A.I.Goncharov and T.S.Sachko, Khim.-Farm.Zh. 1972, 6(1), 29.

43. I.S.Shulga, A.K.Sukhomlinov, A.I.Goncharov and E.M.Dikaya, Khim.-Farm.Zh. 1974, 8(4), 16.

44. I.S.Shulga, A.K.Sukhomlinov, A.I.Goncharov and E.M.Dikaya, Farm. Zh. (Kiev) 1974, 29(2), 27.

45. A.K.Sukhomlinov, A.D.Tarusin, I.Yu.Kholupyak and T.S.Sachko, Khim.-Farm.Zh. 1973, 7(4), 19.

46. I.S.Shulga, A.K.Sukhomlinov, A.I.Goncharov and E.M.Dikaya, Khim.-Farm.Zh. 1974, 8(10), 6.

47. S.M.Deshpande, K.C.Datta and A.K.Singh, J.Indian Chem.Soc. 1975, 52(8), 746.

48. J.Barbet, B.P.Roques and J.-B.Le Pecq, C.R.Acad.Sci.Paris, Ser. D 1975, 281, 851.

49. T.Singh, R.G.Stein and J.H.Biel, J.Med.Chem. 1973, 16(1), 89.

50. V.P.Sergovskaya, V.I.Zakharova, L.O.Rusetskii, V.M.Dorokhova and I.Velinlaev, U.S.S.R. Pat. 380,656; through Otkrytia, Izobret.,Prom.Obraztsy,Tovarnye Znaki 1973, 50(21), 88.

51. J.T.Stewart, J. Pharm. Sci. 1973, 62(8), 1357.

52. J.T.Stewart and D.M.Shepherd, J.Med.Chem. 1970, 13(4), 762.

53. A.N.Gaidukevich, A.I.Goncharov and E.M.Dikaya, Khim.-Farm.Zh. 1973, 7(7), 14.

54. A.N.Gaidukevich, G.S.Bashura, I.M.Piercev, V.P.Shtuchnaya, A.F.Piminov, N.I.Filipchik and L.W.Lysenko, Khim.-Farm. Zh. 1975, 9(6), 25.

55. A.N.Gaidukevich, G.S.Bashura, M.K.Pilipenko, V.P.Shtuchnaya, S.G.Leonova and A.I.Pyatikop, Khim.-Farm.Zh. 1976, 10(1), 112.

56. A.N.Gaidukevich, Yu.L.Goncharenko, V.P.Shtuchnaya and I.Yu.Kholupyak, Khim.Farm.Zh. 1976, 10(7), 33.

57. A.N.Gaidukevich, S.G.Leonova and A.F.Perepelitsa, Khim.-Farm.Zh. 1976, 10(12), 31.

58. V.N.Konyukhov, G.S.Sakovich, L.F.Lipatova, D.P.Shrayer, E.G.Kovalev and Z.V.Pushkareva, Khim.-Farm.Zh. 1974, 8(7), 19.

59. A.DeLeenheer, J.E.Sinsheimer and J.H.Burckhalter, J. Pharm. Sci. 1972, 61(2), 273.

60. J.E.Sinsheimer, V.Jagodic, Lj.Polak, D.D.Hong and J.H.Burckhalter, J. Pharm. Sci. 1975, 64(6), 925.

61. R.M.Acheson and C.W.C.Harvey, J.Chem.Soc., Perkin Trans. I 1976(5), 465.

62. B.K.Sinha, R.L.Cysyk, D.B.Millar and C.F.Chignell, J. Med. Chem. 1976, 19(8), 994.

63. I.M.Nahib, Swedish Pat. 13,236/71.

64. N.S.Drozdov and O.M.Cherntzov, J. Gen. Chem. (U.S.S.R.) 1935, 5, 1576; through Chem. Abs. 1936, 30, 2195.

65. A.Ledóchowski and S.Skonieczny, Roczniki Chem. 1973, 47(9), 1577.

66. Idem, Roczniki Chem. 1975, 49(6), 891.

67. A.Ledóchowski, Materia Med.Polona 1976, 8(3), 237.

68. A.A.Abou Ouf, A.F.Youssef and A.M.Abdel Aleem, Egypt. J. Pharm. Sci. 1972, 13(1), 177 and 187; through Chem. Abs. 1974, 80, 59841 and 59842.

69. V.T.Skripkina, N.N.Dykhanov, V.P.Maksimets and L.D.Shcherbak, Khim.Geterotsikl.Soedin. 1971, 7(1), 15.

70. I.Nahib, M.Nasr and M.A.Badawi, J.Pharm.Sci. 1972, 61(9), 1500.

71. R.Neeb, Ger. Pat. 1,952,086.

72. H.Shindo and K.Kurosawa, J. Pat. 73 22,611.

73. O.J.Magidson and A.M.Grigorovski, Ber. 1936, 69, 396;

see also D.L.Hammick, S.F.Mason and G.W.Meacock, J. Chem. Soc. 1952, 4745.

74. K.C.Tsou, S.Ledis, E.Steiger and R.Nietrzeba, J. Pharm. Sci. 1975, 64(8), 1418.

75. A.DeLeenheer, J.E.Sinsheimer and J.H.Burckhalter, J. Pharm. Sci. 1972, 61(10), 1659.

76. E.F.Elslager, N.F.Haley, J.R.McLean, S.C.Perricone, D.Potoczak, H.Veloso, D.F.Worth and R.H.Wheelock, J. Med. Chem. 1971, 14(9), 782.

77. M.E.Konshin, Khim.Geterotsikl.Soedin. 1970(7), 974.

78. Idem, Khim.Geterotsikl.Soedin. 1970(9), 1242.

79. M.E.Konshin and P.A.Petyukhin, Khim.-Farm.Zh. 1971, 5(11), 10.

80. M.E.Konshin, Khim.Geterotsikl.Soedin. 1973(4), 528.

81. Idem, Khim.Geterotsikl.Soedin. 1974(7), 966.

82. Idem, Khim.Geterotsikl.Soedin. 1975(3), 291; and references cited therein.

83. J.E.Sinsheimer, D.D.Hong and J.H.Burckhalter, J. Pharm. Sci. 1969, 58(6), 1041.

84. J.E.Sinsheimer, D.D.Hong, J.T.Stewart, M.L.Fink and J.H.Burckhalter, J. Pharm. Sci. 1971, 60(1), 141.

85. A.DeLeenheer, J.E.Sinsheimer and J.H.Burckhalter, J. Pharm. Sci. 1972, 61(2), 273.

86. Idem, J. Pharm. Sci. 1973, 62(8), 1370.

87. C.L.Zirkle, Ger. Pat. 1,470,245.

88. M.Ionescu, M.Vlassa and I.Goia, J. Prakt. Chem. 1972, 314(3-4), 441.

89. M.Ionescu and M.Vlassa, Roumanian Pat. 57,902.

90. G.S.Sakovich, Z.V.Pushkareva, V.N.Konyukhov, T.A.Bandurina and A.S.Barybin, Khim.-Farm.Zh. 1972, 6(4), 17.

91. A.C.Mair and M.F.G.Stevens, J. Chem. Soc., Perkin Trans. I 1972(1), 161.

92. (a) G.A.Reynolds, F.J.Rauner and D.J.McClune, Fr. Pat. 1,511,485; through Chem. Abs. 1969, 70(26), 120041.
(b) N.A.Orlova, L.L.Dmitrieva, T.N.Gerasimova and E.P.Fokin, Izv.Sib.Otd.Akad.Nauk SSSR,Ser.Khim.Nauk 1976(3), 114.

93. H.J.-M.Dou, G.Vernin and J.Metzger, Bull. soc. chim. France 1971(12), 4593.

94. A.Clerici, F.Minisci and O.Porta, Tetrahedron 1974, 30(23/24), 4201; and references cited therein.

95. F.Minisci, R.Mondelli, G.P.Gardini and O.Porta, Tetrahedron 1972, 28(9), 2403.

96. F.Minisci, A.Selva, O.Porta, P.Barilli and G.P.Gardini, Tetrahedron 1972, 28(9), 2415.

97. F.Minisci, R.Bernardi, F.Bertini, R.Galli and M.Perchinommo, Tetrahedron 1971, 27(15), 3575.

98. J.M.Anderson and J.K.Kochi, J. Am. Chem. Soc. 1970, 92(6), 1651; idem, J. Org. Chem. 1970, 35(4), 986.

99. Y.Yamamoto, T.Nisimura and H.Nozaki, Bull. Chem. Soc. Japan 1971, 44(2), 541.

100. N.Miyamoto, S.Isiyama, K.Utimoto and H.Nozaki, Tetrahedron Letts. 1971(48), 4597.

101. V.E.Posazhennikova, O.N.Chupakhin and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1970(10), 1384.

102. O.N.Chupakhin, V.E.Kirichenko and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1974(8), 1116.

103. V.E.Kirichenko and O.N.Chupakhin, Khim.Geterotsikl.Soedin. 1974(5), 675.

104. A.K.Sheinkman, S.G.Potashnikova and S.N.Baranov, Zh. Org. Khim. 1971, 7(7), 1550.

105. Idem, U.S.S.R. Pat. 292,479; through Otkrytiya,Izobret., Prom.Obraztsy, Tovarnye Znaki 1971, 48(29), 218.

106. Idem, U.S.S.R. Pat. 327,197; through Otkrytiya,Izobret. Prom.Obraztsy, Tovarnye Znaki 1972, 49(5), 69.

107. S.G.Potashnikova, V.G.Rybalko, I.V.Kurkurina and A.K.Sheinkman, Metody Poluch. Khim. Reaktivov Prep. 1971(23), 137.

108. A.K.Sheinkman, A.K.Tokarev, S.G.Potashnikova, A.A.Deikalo, A.P.Kucherenko and S.N.Baranov, Khim.Geterotsikl.Soedin. 1971(5), 643.

109. T.Kato, T.Chiba and M.Daneshtalab, Heterocycles 1974, 2(3), 315.

110. C.F.Schwender and R.E.Pike, U.S. Pat. 3,936,457.

111. V.M.Kurilenko, L.P.Basova, O.N.Chupakhin and V.E.Kirichenko, Khim.-Farm.Zh. 1975, 9(5), 12.

112. I.Ya.Postovskii, V.E.Posazhennikova, O.N.Chupakhin and E.P.Darienko, Khim.Geterotsikl.Soedin. 1971(8), 1090.

113. L.I.Gribova, A.I.Abramov, A.N.Mezentsev and M.K.Berestenko, Zh. Vses. Khim. Obshchest. 1971, 16(5), 582.

114. Idem, Zh. Prikl. Spektrosk. 1971, 15(1), 163.

115. T.N.Vasilevskaya, I.I.Baturina, M.I.Kollegova, T.N.Gerasimova and V.A.Barkhash, Zh. Org. Khim. 1971, 7(6), 1230.

116. M.Jawdosiuk, J.Czyżewski and M.Mąkosza, J. Chem. Soc., Chem. Comm. 1973(20), 794.

117. B.M.Mikhailov, V.A.Dorokhov and O.G.Boldyreva, Izv. Akad. Nauk SSSR, Ser. Khim. 1973(11), 2643.

118. A.N.Saverchenko, V.A.Kaminskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1973(3), 384.

119. M.R.Bendall, J.B.Bremner and J.F.W.Fay, Aust. J. Chem. 1972, 25(11), 2451.

120. J.L.Brazier, D.Deruaz, J.M.Rouzioux and A.Badinand, J. Eur. Toxicol. 1973, 6(1), 24.

121. J.Gostoli, Ger. Pat. 2,123,569.

122. H.Blattner and W.Schindler, Swiss Pat. 547,815.

123. Idem, Swiss Pat. 545,805.

124. M.Hirobe and T.Ozawa, Tetrahedron Letts. 1971(47), 4493.

125. T.Ozawa, Y.Iitaka, M.Hirobe and T.Okamoto, Chem. Pharm. Bull. 1974, 22(9), 2069.

126. A.P.Kucherenko, S.G.Potashnikova, S.S.Radkova, S.N.Baranov, A.K.Sheinkman and N.V.Volbushko, Khim.Geterotsikl.Soedin. 1974(9), 1257.

127. G.E.Ivanov, Khim.Geterotsikl.Soedin. 1973(5), 663.

128. O.Tsuge, A.Torii and T.Tomita, Nippon Kagaku Zasshi 1969, 90(12), 1263; through Chem. Abs. 1970, 43(9), 2920.

129. O.Tsuge and A.Torii, Bull.Chem.Soc.Japan 1970, 43(9), 2920.

130. Idem, Bull.Chem.Soc.Japan 1972, 45(10), 3187.

131. Idem, Bull.Chem.Soc.Japan 1976, 49(4), 1138.

132. Idem, Org.Prep.Preced.Int. 1972, 4(4), 153.

133. Idem, Bull.Chem.Soc.Japan 1973, 46(1), 283.

134. A.Torii, H.Higashiuchi and O.Tsuge, Heterocycles 1974, 2(5), 615.

135. A.Torii and O.Tsuge, Heterocycles 1975, 3(7), 557.

136. R.B.Homer and M.Shinitzky, Macromolecules 1968, 1(11-12), 469.

137. J.T.Stewart and R.E.Gammans, J.Pharm.Sci. 1975, 64(6), 1061.

138. A.A.Deikalo, A.K.Sheinkman and S.N.Baranov, Khim.Geterotsikl.Soedin. 1972(10), 1359.

139. V.N.Konyukhov, G.S.Sakovich, T.N.Aksenova, T.A.Bandurina, L.B.Radina, Z.V.Pushkareva, N.A.Lesnaya and A.S.Barybin, Khim.-Farm.Zh. 1976, 10(7), 56.

140. Ref. 10, p. 68 and Ref. 11, p. 82.

141. C.Tashiro, Jap. Pat. 73 52,777.

142. K.M.Baker, A.Frigerio, P.L.Morselli and G.Pifferi, J. Pharm. Sci. 1973, 62(3), 475.

143. E.Rapaport, M.W.Cass and E.H.White, J. Am. Chem. Soc. 1972, 94(9), 3160.

144. Idem, J. Am. Chem. Soc. 1972, 94(9), 3153.

145. M.Cârje, Rev. Roum. Chim. 1973, 18(6), 1013.

146. A.Arnone, M.Cecere, R.Galli, F.Minisci, M.Perchinunno, O.Porta and G.Gardini, Gazz.Chim.Ital. 1973, 103(1), 13.

147. M.Cârje, Rev. Roum. Chim. 1974, 19(2), 249.

148. J.W.Happ and E.G.Janzen, J. Org. Chem. 1970, 35(1), 96.

149. K.E.Whitaker and H.R.Snyder, J.Org.Chem. 1970, 35(1), 30.

150. R.B.Chapas, R.F.Nystrom and H.R.Snyder, J. Org. Chem. 1972, 37(2), 314.

151. Y.Kobayashi, I.Kumadaki and H.Sato, J. Org. Chem. 1972, 37(23), 3588.

152. A.K.Sheinkman, S.G.Potashnikova and S.N.Baranov, Khim.Geterotsikl.Soedin. 1969(4), 563.

153. Idem, Zh. Org. Khim. 1970, 6(3), 614.

154. Idem, Metody Poluch. Khim. Reaktivov Prep. 1971(23), 49.

155. A.K.Sheinkman, Khim.Geterotsikl.Soedin. 1974(1), 3.

156. V.A.Trofimov, O.N.Chupakhin and Z.V.Pushkareva, U.S.S.R. Pat. 292,976; through Otkrytiya, Izobret., Prom.Obraztsy, Tovarnye Znaki 1971, 48(5), 99.

157. O.N.Chupakhin, V.N.Charushin and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1975(11), 1578.

158. Idem, Zh. Org. Khim. 1976, 12(7), 1553.

159. V.A.Trofimov, O.N.Chupakhin and Z.V.Pushkareva, U.S.S.R. Pat. 271,697; through Otkrytiya, Izobret., Prom.Obraztsy, Tovarnye Znaki 1970, 47(18), 61.

160. V.A.Trofimov, O.N.Chupakhin, Z.V.Pushkareva and V.L.Rusinov, Khim.Geterotsikl.Soedin. 1971(1), 112.

161. V.L.Rusinov, O.N.Chupakhin, V.A.Trofimov, M.I.Kollegova and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1972(2), 216.

162. O.N.Chupakhin, Yu.N.Sheinker, Z.V.Pushkareva, V.A.Trofimov, E.G.Kovalev and V.G.Kharchuk, Khim.Geterotsikl.Soedin. 1973(4), 535.

163. A.K.Sheinkman, V.A.Ivanov, N.A.Klyuev and G.A.Maltseva, Zh. Org. Khim. 1973, 9(12), 2550.

164. O.N.Chupakhin, V.A.Trofimov and Z.V.Pushkareva, Dokl. Akad. Nauk SSSR 1969, 188(2), 376.

165. Idem, Khim.Geterotsikl.Soedin. 1970(12), 1674.

166. O.N.Chupakhin, V.L.Rusinov, I.Ya.Postovskii, V.N.Charushin and A.G.Filimonova, U.S.S.R. Pat. 431,165; through Otkrytiya, Izobret., Prom.Obraztsy, Tovarnye Znaki 1974, 51(21), 84.

167. O.N.Chupakhin, I.Ya.Postovskii, V.L.Rusinov and V.N.Charushin, Khim.Geterotsikl.Soedin. 1975(3), 387.

168. O.N.Chupakhin, V.N.Shilov, I.Ya.Postovskii and V.A.Trofimov, Khim.Geterotsikl.Soedin. 1976(2), 266.

169. O.N.Chupakhin, I.Ya.Postovskii, V.N.Shilov and V.A.Trofimov, Khim.Geterotsikl.Soedin. 1975(6), 817.

170. A.K.Sheinkman and G.V.Samoilenko, U.S.S.R. Pat. 434,076; through Otkrytiya,Izobret.,Prom.Obraztsy, Tovarnye Znaki 1974, 51(24), 38.

171. A.K.Sheinkman, S.G.Potashnikova and S.N.Baranov, Metody Poluch. Khim. Reaktivov Prep. 1971(23), 77.

172. Idem, Khim.Geterotsikl.Soedin. 1970(9), 1292.

173. A.K.Sheinkman, A.N.Kost, S.G.Potashnikova, A.O.Ginzburg and S.N.Baranov, Khim.Geterotsikl.Soedin. 1971(5), 648.

174. A.K.Sheinkman and A.A.Deikalo, Khim.Geterotsikl.Soedin. 1970(1), 126.

175. Idem, Khim.Geterotsikl.Soedin. 1971(12), 1654.

176. A.R.Katritzky, J.Lewis, G.Musumarra and G.Ogretir, Chim. Ind. (Milan) 1976, 38(5), 381.

177. A.K.Sheinkman, A.A.Deikalo, T.V.Stupnikova, N.A.Klyuev and G.A.Maltseva, Khim.Geterotsikl.Soedin. 1972(8), 1099.

178. A.K.Sheinkman, A.A.Deikalo, T.V.Stupnikova and S.N.Baranov, Khim.Geterotsikl.Soedin. 1972(2), 284.

179. G.S.Sakovich, V.N.Konyukhov, T.A.Bandurina, Z.V.Pushkareva, G.N.Koltun, V.F.Degtyarev, V.E.Blokhin, M.A.Presnov,

A.L.Konovaleva and A.S.Barybin, Khim.-Farm.Zh. 1973, 7(3), 17.

180. A.Mukoo, Y.Mori and H.Morishita, Jap.Patents 76 04,181 and 76 04,182; through Chem.Abs.1976, 84(25),180086 and 180087.

181. Idem, Ger. Pat. 2,522,993.

182. Yu.A.Rozin, V.E.Blokhin, Z.V.Pushkareva and M.E.Sukhova, Khim.Geterotsikl.Soedin. 1972(5), 681.

183. Yu.A.Rozin, V.E.Blokhin, Z.V.Pushkareva, V.I.Yelin and M.E.Sukhova, Khim.Geterotsikl.Soedin. 1973(8), 1105.

184. V.I.Vysotskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1976(3), 383; and references cited therein.

185. V.A.Kaminskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1974(10), 1434.

186. A.N.Saverchenko, V.A.Kaminskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1973(3), 384.

187. N.Barbulescu, F.Potmischil and G.Badita, Chem.Ber. 1971, 104(3), 787.

188. A.H.Moustafa, R.H.Zahran and N.F.Eweiss, J. Prakt. Chem. 1975, 317(4), 545.

189. H.Hoberg and A.Milchereit, Justus Liebiegs Ann. Chem. 1972, 766, 146; and references cited therein.

190. N.A.Klyuev, R.A.Khmelnitskii, O.N.Chupakhin, G.A.Maltseva, V.L.Rusinov and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1975(7), 983.

191. N.A.Klyuev, G.A.Maltseva, R.A.Khmelnitskii, O.N.Chupakhin and V.L.Rusinov, Zh. Org. Khim. 1976, 12(6), 1154.

192. I.A.Selby, Ref. 11, p. 433.

193. Y.Miyashita, S.Niizuma and M.Koizumi, Bull. Chem. Soc. Japan 1970, 43(11), 3435.

194. K.Nakamaru, S.Niizuma and M.Koizumi, Bull. Chem. Soc. Japan 1971, 44(5), 1256.

195. Idem, Z. Phys. Chem. N.F. 1970, 73(1-3), 113.

196. Idem, Chem. Letts. 1972(1), 59.

197. Idem, Bull. Chem. Soc. Japan 1972, 45(8), 2445.

198. D.G.Whitten and Y.J.Lee, J.Am.Chem.Soc. 1971, 93(4), 961.

199. A.Castellano, J.-P.Catteau, A.Lablache-Combier, B.Planckaert and G.Allan, Khim.Geterotsikl.Soedin. 1974(7), 867; and references cited therein.

200. G.Vermeersch, N.Febvay-Garot, S.Caplain and A.Lablache-Combier, Tetrahedron Letts. 1974(36), 3127.

201. G.Vermeersch, N.Febvay-Garot, S.Caplain and A.Lablache-Combier, Tetrahedron 1975, 31(8), 867.

202. M.Hoshino, S.Niizuma and M.Koizumi, Bull.Chem.Soc.Japan 1972, 45(10), 2988.

203. M.Hoshino and M.Koizumi, Bull.Chem.Soc.Japan 1973, 46(3), 745.

204. V.Zanker and G.Prell, Ber.Busenges.Physik.Chem. 1969, 73(8-9), 791.

205. A.Castellano, J.-P.Catteau and A.Lablache-Combier, J. Chem. Soc., Chem. Comm. 1972(20), 1207.

206. Idem, Can. J. Chem. 1973, 51(21), 3508.

207. Idem, J. Phys. Chem. 1976, 80(23), 2614.

208. S.Yamada, M.Ishikawa and C.Kaneko, Chem.Pharm.Bull. 1975, 23(11), 2818; idem, Tetrahedron Letts. 1972(11), 971 and 977; idem, Tetrahedron Letts. 1970(27), 2329.

209. Idem, J. Chem. Soc., Chem. Comm. 1972(19), 1093.

210. R.Noyori, M.Kato, H.Kawanisi and H.Nozaki, Tetrahedron 1969, 25(5), 1125.

211. R.Kaptein, J. Chem. Soc., Chem. Comm. 1971(14), 732.

212. J.Libman, J. Chem. Soc., Chem. Comm. 1976(6), 198.

213. R.S.Davidson, P.F.Lambeth and M.Santhanam, J. Chem. Soc., Perkin Trans. II 1972(15), 2351.

214. N.C.Yang, K.Srinivasachar, B.Kim and J.Libman, J. Am. Chem. Soc. 1975, 97(17), 5006.

215. T.Sasaki, K.Kanematsu, I.Ando and O.Yamashita, J. Am. Chem. Soc. 1976, 98(9), 2686.

216. A.F.Pozharskii and A.A.Konstantinchenko, Khim.Geterotsikl.Soedin. 1972(12), 1673.

217. O.N.Chupakhin, V.L.Rusinov and I.Ya.Postovskii, Khim.Geterotsikl.Soedin. 1972(2), 284.

218. G.E.Ivanov and V.A.Izmailskii, Khim.Geterotsikl.Soedin. 1970(8), 1119.

219. C.S.Sheppard and R.Levine, J.Heterocycl.Chem. 1964, 1(1), 64.

220. R.Levine and C.S.Sheppard, J. Org. Chem. 1974, 39(24), 3556.

221. H.Nozaki, T.Nisimura and Y.Yamamoto, Bull.Chem.Soc.Japan 1972, 45(1), 301.

222. G.Wittig, S.Fisher and M.Tanaka, Justus Liebigs Ann. Chem. 1973(7), 1075.

223. F.Bertini, T.Carona, A.Citterio, L.Grossi and F.Minisci, Chim. Ind. (Milan) 1974, 56(4), 272.

224. L.Birkofer and N.Ramadan, Chem. Ber. 1975, 108(9), 3105.

225. D.Redmore, U.S. Pat. 3,816,428.

226. D.Redmore, U.S. Pat. 3,830,815.

227. Idem, J. Org. Chem. 1969, 34(5), 1420.

228. A.K.Sheinkman, G.V.Samoilenko and S.N.Baranov, Dokl. Akad. Nauk SSSR 1971, 196(6), 1377.

229. A.K.Sheinkman, G.V.Samoilenko and N.A.Klyuev, Zh. Obshch. Khim. 1974, 44(7), 1472.

230. C.Tashiro and T.Sakuragi, Jap. Pat. 73 12,747.

231. C.Tashiro, Jap. Pat. 73 52,776.

232. K.-W.Lee, L.A.Singer and K.D.Legg, J. Org. Chem. 1976, 41(16), 2685.

233. E.G.Janzen, J.B.Pickett, J.W.Happ and W.DeAngelis, J. Org. Chem. 1970, 35(1), 88.

234. I.Agranat and Y.Tapuhi, J.Am.Chem.Soc. 1976, 98(2), 615.

235. C.Kaiser, P.J.Fowler, D.H.Tedeschi, B.M.Lester, E.Garvey, and C.L.Zirkle, J. Med. Chem. 1974, 17(1), 57.

236. J.W.Bunting and W.G.Meathrel, Can.J.Chem. 1974, 52(6), 981.

237. Idem, Can.J.Chem. 1973, 51(12), 1965.

238. Idem, Can.J.Chem. 1972, 50(6), 917.

239. V.L.Rusinov, O.N.Chupakhin, I.Ya.Postovskii and L.M.Osenova, Khim.Geterotsikl.Soedin. 1973(9), 1291.

240. O.N.Chupakhin, I.Ya.Postovskii, V.L.Rusinov, L.M.Naumova and N.A.Klyuev, Zh. Org. Khim. 1975, 11(6), 1324.

241. O.N.Chupakhin, I.Ya.Postovskii, V.L.Rusinov and L.I.Mikisheva, Khim.Geterotsikl.Soedin. 1975(6), 814.

242. G.A.Digenis, J. Pharm. Sci. 1969, 58(3), 335.

243. G.A.Digenis and E.O.Magarian, J.Pharm.Sci. 1969, 58(8), 1026.

244. M.B.Shambhu, R.R.Koganty and G.A.Digenis, J. Med. Chem. 1974, 17(8), 805.

245. G.A.Digenis and H.W.Whitlock,Jr., J.Pharm.Sci. 1972, 61(2), 206.

246. G.A.Digenis, S.Shakhshir, M.A.Miyamoto and H.B.Kostenbauder, J.Pharm.Sci. 1976, 65(2), 247.

247. D.J.Creighton, J.Haidu, G.Moser and D.S.Sigman, J.Am.Chem.Soc. 1973, 95(20), 6855.

248. J.J. Steffens and D.M.Chipman, J.Am.Chem.Soc. 1971, 93(24), 6694.

249. A.K.Colter, G.Saito, F.J.Sharom and A.P.Hong, J.Am.Chem.Soc. 1976, 98(24), 7833.

250. I.M.Sosonkin, V.A.Subbotin, V.N.Charushin and O.N.Chupakhin, Dokl. Akad. Nauk SSSR 1976, 229(4), 888.

251. V.I.Alekseev, V.A.Kaminskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1976(7), 957; idem, Khim.Geterotsikl.Soedin. 1975(2), 235.

252. A.N.Saverchenko, Z.R.Bekkerova, V.A.Kaminskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1974(2), 243.

253. R.J.Highet and J.F.Biellmann, J.Org.Chem. 1972, 37(23), 3731.

254. S.Inayama and K.Mamoto, Jap. Patents 75 157,378 and 75 157,379; through Chem.Abs. 1976, 85(13), 94242 and 85(15), 108558.

255. E.R.Zaks, N.G.Leshenyuk and L.S.Efros, Khim.Geterotsikl.Soedin. 1973(4), 539.

256. Y.H.Wu and W.G.Lobeck,Jr., U.S. Pat. 3,946,004.

257. J.Casanova and M.Geisel, Inorg.Chem. 1974, 13(12), 2783.

258. J.M.F.Gagan, Ref. 11, p. 141.

259. B.Wysocka-Skrzela and A.Ledóchowski, Roczniki Chem. 1976, 50(1), 127.

260. M.Ionescu and I.Hopartean, Stud.Univ.Babes-Bolyai, Ser.Chem. 1972, 10(2), 105.

261. M.Ionescu, I.Hopartean and M.Kezdi, Stud.Univ.Babes-Bolyai, Ser.Chem. 1973, 18(1), 25.

262. L.E.Kholodov, N.M.Merzlyakova, E.A.Rudzit and D.A.Kulikova, Khim.-Farm.Zh. 1975, 9(2), 19.

263. H.S.Bajaj, R.D.Desai and G.S.Saharia, J.Indian Chem.Soc. 1975, 52(10), 962.

264. D.K.C.Hodgeman and R.H.Prager, Aust.J.Chem. 1972, 25(1), 191.

265. R.M.Acheson and R.G.Bolton, J.Chem.Soc., Perkin Trans. I 1975(7), 650.

266. B.Rindone and C.Scolastico, J.Chem.Soc., Perkin Trans. I 1975(14), 1398.

267. H.Inoue, S.Kawahara and E.Imoto, Chem.Letts. 1972(3), 207.

268. G.E.Gream, D.K.C.Hodgeman and R.H.Prager, Aust. J. Chem. 1972, 25(3), 569.

269. D.K.C.Hodgeman and R.H.Prager, Aust.J.Chem. 1972, 25(3), 585.

270. Idem, Aust.J.Chem. 1972, 25(8), 1751.

271. R.H.Prager and D.K.C.Hodgeman, Aust.J.Chem. 1972, 25(8), 1761.

272. J.R.Cowan, D.K.C.Hodgeman and R.H.Prager, Aust.J.Chem. 1972, 25(8), 1351.

273. J.Schneider, E.L.Evans, E.Grunberg and R.I.Fryer, J. Med. Chem. 1972, 15(3), 266.

274. A.Chatterjee and D.Ganguly, Phytochemistry 1976, 15(8), 1303.

275. T.A.Crabb, Annu. Rep. NMR Spectrosc. 1975, 6A, 249; through Chem. Abs. 1976, 85(3), 17704.

276. M.F.Grundon, Alkaloids (London) 1976(6), 103.

277. A.Ledóchowski, S.Skonieczny, A.Głowacki and J.Mogielnicki, Roczniki Chem. 1977, 51(2), 359.

278. M.J.Kramer, R.Cleeland and E.Grunberg, Antimicrob.Agents Chemother. 1976, 9(2), 233; through Chem. Abs. 1976, 84(21), 144795.

279. I.M.Roushdi, A.A.Mikhail and I.Chaaban, Pharm. 1976, 31(6), 406.

280. B.K.Manukin, W.Huber and E.Glanzman, Helv.Chim.Acta 1975, 58(1), 110.

281. S.Hayashi and N.Ishikawa, Nippon Kagaku Kaishi, 1973(7), 1319; through Chem. Abs. 1973, 79(13), 78576.

282. C.M.Jenkins, A.E.Pedler and J.C.Tatlow, Tetrahedron 1971, 27(12), 2557.

283. I.D.Postescu and D.Suciu, J.Prakt.Chem. 1976, 318(3), 515.

284. R.H.Prager, Aust.J.Chem. 1975, 28(2), 455.

285. I.Goia and M.Ionescu, Rev.Roum.Chim. 1970, 15(8), 1233.

286. Idem, Stud.Univ.Babes-Bolyai,Ser.Chem. 1972, 17(1), 63.

287. I.Panea and M.Ionescu, Stud.Univ.Babes-Bolyai,Ser.Chem. 1972, 17(1), 103.

288. Idem, Stud.Univ.Babes-Bolyai,Ser.Chem. 1973, 18(1), 11.

289. M.Ionescu, I.Hopartean and S.Mager, Stud.Univ.Babes-Bolyai,Ser.Chem. 1975, 20(1), 50.

290. I.Panea, I.Goia and M.Ionescu, Rev.Roum.Chim. 1972, 17(8), 1423.

291. K.V.Stanovkina, I.L.Shegal and A.Yu.Ermishov, U.S.S.R. Pat. 514,827; through Otkrytiya,Izobret.,Prom.Obraztsy,

Tovarnye Znaki 1976, 53(19), 56.

292. R.D.Chambers, R.Daniels, W.K.R.Musgrave and P.L.Russell, J. Chem. Soc., Perkin Trans. I 1976(10), 1069.

293. R.Y.Ning, P.B.Madan, J.F.Blount and R.I.Fryer, J. Org. Chem. 1976, 41(21), 3406.

294. J.H.Markgraf, M.-K.Ahn, C.G.Carson,III and G.A.Lee, J. Org. Chem. 1970, 35(11), 3983.

295. I.Goia and M.Ionescu, Stud.Univ.Babes-Bolyai,Ser.Chem. 1972, 17(1), 77.

296. M.Ionescu, I.Goia and M.Vlassa, Rev.Roum.Chim. 1970, 15(11), 1785.

297. I.Panea, I.Goia and M.Ionescu, Rev.Roum.Chim. 1972, 17(8), 1423.

298. I.Goia and M.Ionescu, Stud.Univ.Babes-Bolyai,Ser.Chem. 1971, 16(2), 65.

299. V.P.Maksimets and O.N.Popilin, Khim.Geterotsikl.Soedin. 1970(2), 191.

300. M.Gniazdowski, L.Szmigiero, K.Sląska, B.Jaros-Kamińska and E.Ciesielska, Mol. Pharmacol. 1975, 11(5), 310.

301. B.F.Cain, W.R.Wilson and B.C.Baguley, Mol. Pharmacol. 1976, 12(12), 1027.

302. A.K.Sheinkman, G.V.Samoilenko and S.N.Baranov, Zh. Obshch. Khim. 1970, 40(3), 700.

303. A.K.Sheinkman, S.N.Baranov and G.V.Samoilenko, U.S.S.R. Pat. 333,171; through Otkrytiya,Izobret.,Prom.Obraztsy, Tovarnye Znaki 1975, 52(27), 173.

304. A.B.Demyashkevich and B.M.Uzhinov, Zh. Prikl. Spektrosk. 1974, 21(3), 496.

305. A.A.Krasheninnikov and Yu.A.Panteleev, Teor. Eksp. Khim. 1974, 10(3), 335.

306. H.Böhland and R.Müller, Z. Chem. 1973, 13(2), 72.

307. Idem, Z. Chem. 1974, 14(6), 248.

308. T.V.Moskovkina, V.A.Kaminskii, V.I.Vysotskii and M.N.Tilichenko, Khim.Geterotsikl.Soedin. 1973(6), 826.

309. N.Barbulescu and G.Nicolae, Rev.Chim.(Bucharest) 1971, 22(6), 368; through Chem. Abs. 1971, 75(21), 129638.

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