Tetracyclic Derivatives of Acridine. Heterofused Acridines

Jean-Pierre Galy*, Sandrine Morel and Gérard Boyer

URA CNRS 1411, Faculte des Sciences et Techniques de Saint Jérôme,
Avenue Escadrille Normandie-Niemen, F-13397 Marseille Cédex 20, France

José Elguero

Instituto de Química Médica, C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

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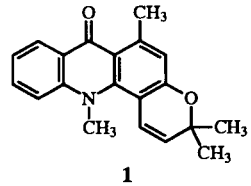
Contents

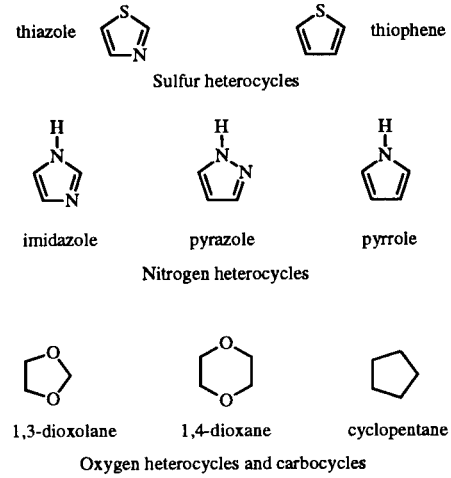
1. Introduction.

In this review we have collected the publications and patents dealing with the synthesis and biological properties of tetracyclic acridines. All these compounds have in common a fourth ring fused to the acridine ring, the fourth ring being a five or six-membered heterocycle or, very seldom, a saturated carbocycle. This last ring often modifies, in an interesting way, the biological activity of acridines; for instance, the alkaloid extracted from the *Rutacea "acronycia baueri"* is a 9-acridinone derivative **1** and due to its antitumor properties it has been marketed as "acronycin" [1].



1

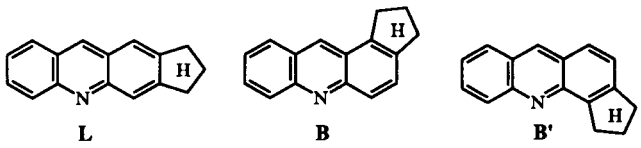
The literature discussed here covers all acridine derivatives (mainly acridines and acridinones) fused to the following classes of cycles:



The nomenclature follows that used in the *Chemicals Abstracts*. One aspect of these tetracycles is especially relevant in this context: their 'linear' **L** or 'bent' **B** (or **B'**) structures.

2. Tetracyclic Sulfur Acridines.

The bibliography of this section covers exclusively thiazoloacridines and thienoacridines with special emphasis on the former.

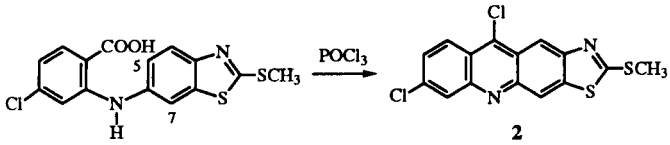


L B B'

a. Thiazoloacridines.

a1. Thiazolo[4,5-*b*]acridine.

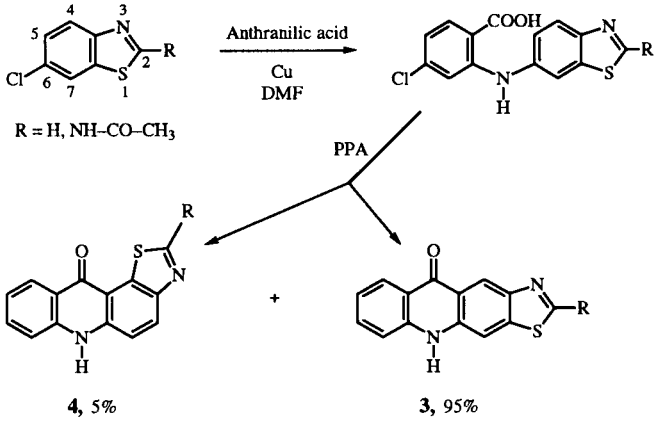
The first compound of this class, 7,10-dichloro-2-methylmercaptothiazolo[4,5-*b*]acridine **2**, was prepared by Taniyama [2] in 1947 by treating 4-chloro-*N*-(2-methylmercaptobenzothiazol-6-yl)anthranilic acid with phosphorus oxychloride.



2

Recently, Taraporewala [3] prepared thiazolo[4,5-*b*]-acridines by condensing anthranilic acid with 6-chlorobenzothiazoles (R = H, NH-CO-CH_3) in a type II Ullmann-Jourdan reaction. Yields were 38% and 47% respectively. Polyphosphoric acid (PPA) cyclization provided the required thiazolo[4,5-*b*]acridines as an isomeric mixture of two compounds, the major one is "linear" thiazolo[4,5-*b*]acridinone **3** (95%) and the minor one is thiazolo[5,4-*a*]acridinone **4** (5%) (Scheme 1).

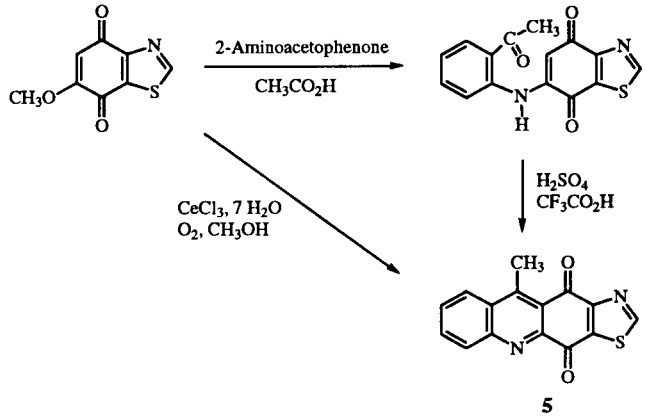
Scheme 1



4, 5% **3**, 95%

10-Methylthiazolo[4,5-*b*]acridine-4,11-dione **5**, an intermediate in the total synthesis of kuanoniamine **A** (a pentacyclic aromatic alkaloid isolated from marine organisms) was prepared from 6-methoxybenzothiazol-4,7-dione treated with 2-aminoacetophenone in refluxing acetic acid for 12 hours to give the anilinoquinone in 39% yield. Afterwards, this quinone was refluxed with concentrated sulfluric acid in trifluoroacetic acid for 75 minutes to furnish the tetracyclic quinone **5** in 36% yield. Another way of cyclization consisted in refluxing 6-methoxybenzothiazole-4,7-dione and benzothiazoldione in methanol containing cesium(III) chloride under air for 18 hours; in these conditions **5** was obtained directly in 73% yield (Scheme 2) [4].

Scheme 2

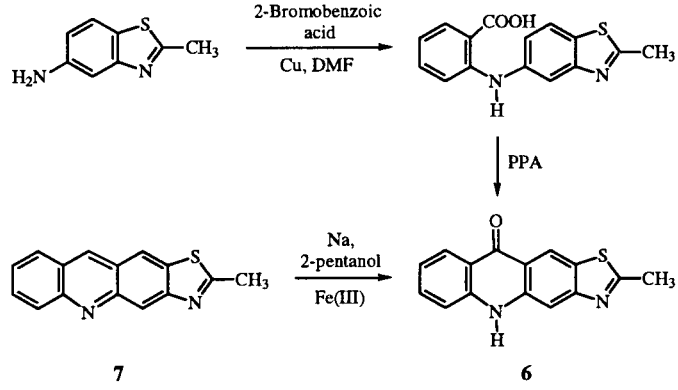


5

a2. Thiazolo[5,4-*b*]acridine.

Condensation of 5-amino-2-methylbenzothiazole in a type I Ullmann-Jourdan reaction afforded *N*-(2-methylbenzothiazol-5-yl)anthranilic acid in a 67% isolated yield. Polyphosphoric acid cyclodehydration provided, in near quantitative yield, a single product identified as the "linear" isomer **6** (Scheme 3). This 9-oxoacridine **6** was finally converted into 2-methylthiazolo[5,4-*b*]acridine **7** by reduction with sodium in 2-pentanol.

Scheme 3



7 **6**

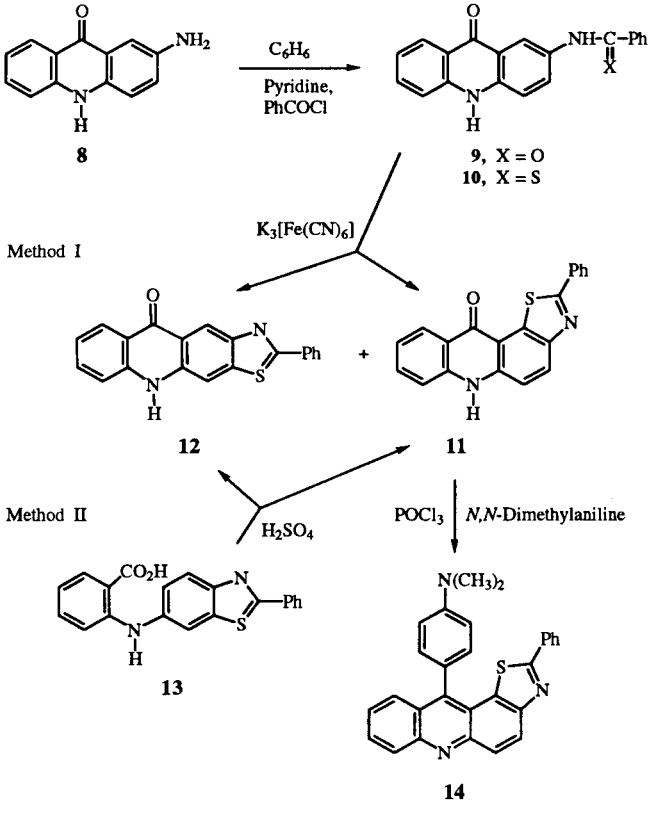
This compound similar to the known antitumor agents adriamycin (doxorubicin) and ellipticine in having a linearly fused tetracyclic ring structure (capable of DNA intercalation), was studied by Taraporevala [5] and proved effective in completely inhibiting the cell proliferation of breast, colon, and lung tumor cell lines at 1.5 μ*M* concentration.

a3. Thiazolo[5,4-*a*]acridine.

Farcasan and Balazs [6] prepared 2-phenylthiazolo-[5,4-*a*]acridinone **11** following two different procedures

(Scheme 4). First method: reacting 2-aminoacridinone **8** with benzoyl chloride in benzene and pyridine, 2-benzamidacridinone **9** was obtained. Treatment of a suspension of this compound with phosphorus pentasulfide in pyridine gave 45% of 2-thiobenzamidothiacridinone **10**. Then, this tetracycle was reacted with a 20% potassium ferricyanide solution at 45° in a mixture of potassium hydroxide/-ethanol to give a mixture of 2-phenylthiazoloacridinones **11** and **12**. Second method: preparing first *N*-(2-phenylbenzothiazol-6-yl) anthranilic acid **13** from 2-chlorobenzoic acid and 6-amino-2-phenylbenzothiazole (Ullmann condensation) and then heating **13** on a water bath for 1 hour in concentrated sulfuric acid also yielded the same mixture of acridinones **11** and **12**. According to these authors, the compound should have the 'bent' thiazolo-[5,4-*a*]acridinone structure **11**, which is reasonable.

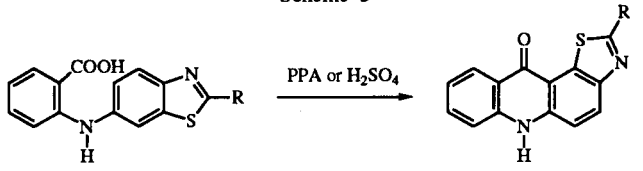
Scheme 4



2-Phenylthiazolo[5,4-*a*]acridinone **11** treated in a steam bath with a mixture of phosphorus oxychloride and *N,N*-dimethylaniline for 2 hours afforded 86% of 2-phenyl-11-(dimethylaminophenyl)thiazolo[5,4-*a*]acridine **14** [6].

Thiazolo[5,4-*a*]acridinones can also be prepared from 6-aminobenzothiazoles (R = H, Me, Cl, NH_2) [7]. These compounds were condensed with potassium *o*-chlorobenzoates in the presence of copper following the Ullmann procedure, to afford *N*-(benzothiazol-6-yl)anthranilic acids in 30-40% yield. These yields were improved using ultrasonics [8] with copper and potassium carbonate in 1-pentanol. Times did not exceed 2 hours and the best results were obtained with a trace of potassium iodide (yields: 60-75%). The last step involves the cyclization of the anthanilic acid either with polyphosphoric acid or sulfuric acid affording thiazoloacridin-9(10*H*)-one [7] which has, according to nmr studies, the 'bent' structure **15** (Scheme 5).

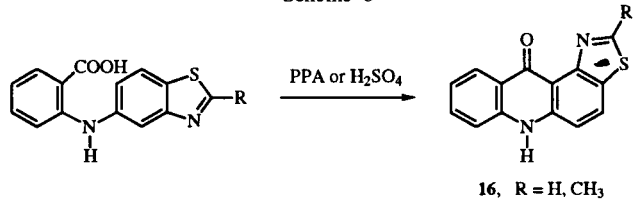
Scheme 5



a4. Thiazolo[4,5-*a*]acridine.

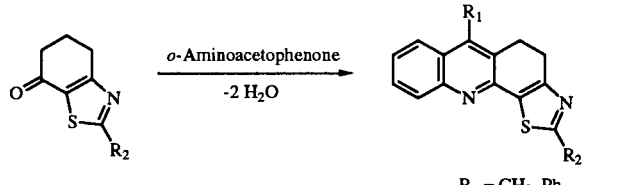
These compounds (Scheme 6) were prepared following the same procedure than the preceding acridines, but starting from the corresponding 2-substituted-5-aminobenzothiazoles and potassium *o*-chlorobenzoate [9]. *N*-(2-Substitutedbenzothiazol-5-yl)anthranilic acids (R = H, CH_3) were purified by repeated recrystallization in acetone (yields fair: 24% and 22% respectively). Cyclization with polyphosphoric acid or sulfuric acid at 100°-110° during 2 hours allows to isolate only the "bent" isomer **16** after methanol crystallization.

Scheme 6



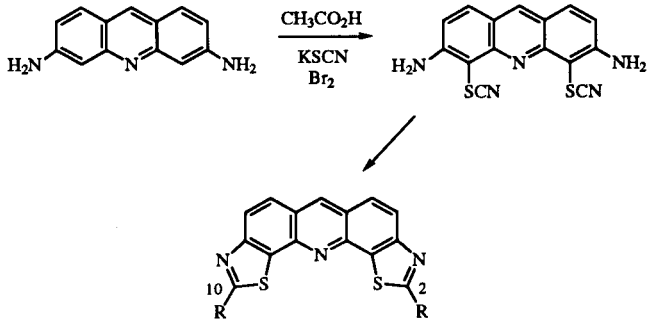
a5. Thiazolo[4,5-*c*]acridine.

Derivatives of dihydrothiazolo[4,5-*c*]acridine **17** were prepared from an *o*-aminoacetophenone/hydrochloric acid and a heterocyclic cyclohexenone [10]. In this way, 2,6-dimethyl and 2-methyl-6-phenyl-4,5-dihydrothiazolo[4,5-*c*]acridines (50% and 70%), were obtained.



a5. Dithiazoloacridine.

Starting from 3,6-diaminoacridine, potassium thiocyanate and bromine in acetic acid, 3,6-diamino-4,5-dithiocyanoacridine was prepared [11]. This intermediate reacted with disodium sulfide and the corresponding alkylating agent to afford a series of dithiazoloacridines **18** disubstituted at positions 2 and 10.

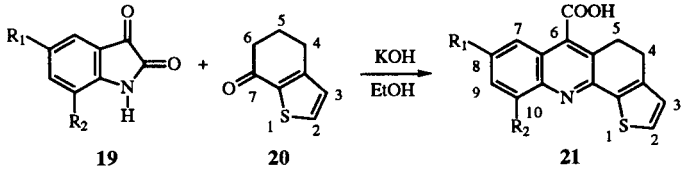


18, R = H, CH_3, NH_2, C_6H_5

b. Thienoacridines.

b1. Thieno[3,2-*c*]acridine.

Buu Hoï and Royer [12] were the first to synthesize 8,10-disubstituted-4,5-dihydrothieno[3,2-*c*]acridines **21** ($R_1 = R_2 = H$, $R_1 = R_2 = CH_3$, $R_1 = CH_3$, $R_2 = H$). These compounds were prepared using the Pfitzinger procedure by condensing substituted isatins **19** with 4,5,6,7-tetrahydro-7-thianaphthenone **20** in potassium hydroxide/ethanol under reflux during 12 hours. In this way, 3,4-dihydrothieno[3,2-*c*]acridine-10-carboxylic acid **21** was obtained (this acid have similar properties as tetrophan, a therapeutic with strychinine-like action). Decarboxylation by heating (320°) afforded the desired 3,4-hydrothieno[3,2-*c*]-acridines.



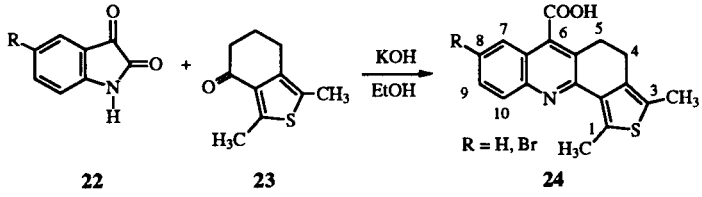
19 **20** **21**

b2. Thieno[3,4-*c*]acridine.

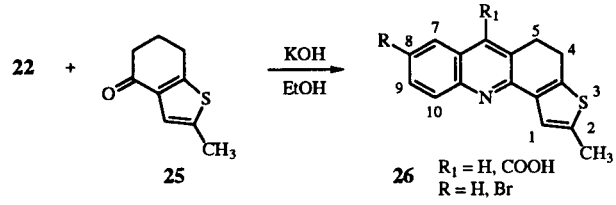
A similar reaction (Pfitzinger-Borsche) but using as starting materials 1,3-dimethyl-6,7-dihydro-4(5*H*)-isothianaphtenone **23** and isatine **22** (24 hours reflux in ethanol with potassium hydroxide) afforded 4,5-dihydro-1,3-dimethylthieno[3,4-*c*]acridine-6-carboxylic acid **24** [13]. Acid **24** was decarboxylated at 330° [13].

b3. Thieno[2,3-*c*]acridine.

4,5-Dihydrothieno[2,3-*c*]acridines **26** were prepared analogously. Isatin **22** and 2-methyl-6,7-dihydro-4(5*H*)-thianaphtenone **25** afforded the carboxylic acid derivatives; these compounds, ($R_1 = CO_2H$, mp 328°), were easily decarboxylated to the corresponding acridines (mp 140°) [13-15].

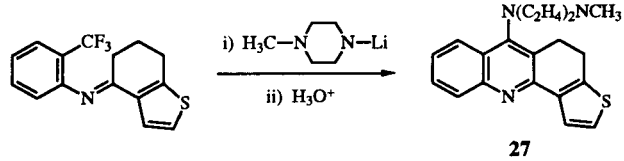


22 **23** **24**



25 **26** R_1 = H, COOH

Another derivative, 4,5-dihydro-6-(4-methyl-1-piperazinyl)thieno[2,3-*c*]acridine **27** was prepared by cyclization of a ketimine with lithium 4-methylpiperazide in diethyl ether at -10° for 30 minutes followed by acid hydrolysis. A yield of 77% was reported [16].



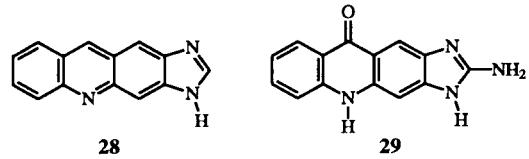
27

3. Tetracyclic Nitrogen Acridines.

a. Imidazoacridines.

a1. Imidazo[4,5-*b*]acridine.

Derivatives of the 2*H*-imidazo[4,5-*b*]acridine ring system **28** quoted in the *Chemical Abstracts Index*, **57**, 1266s (1962) were in fact phenoxazines [17].



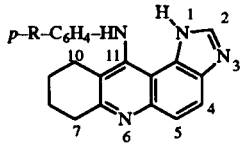
28 **29**

Thus, Taraporewala's report [3], concerning the preparation of 2-amino-1,5-dihydroimidazo[4,5-*b*]acridin-10-one **29** by reacting 2,3-diamino-9-acridinone with cyanogen bromide in dichloromethane, was the first synthesis of this ring system. The synthetic method guarantees that **29** has a 'linear' structure.

a2. Imidazo[4,5-*a*]acridine.

Starting from imidazo[4,5-*f*]quinolines, 7,8,9,10-tetrahydro derivatives **30** substituted by anilines at position 11 were prepared [18]. According to the patent, these compounds

enhanced the immune system response by protection of mice challenged with pseudomonas aeruginosa.

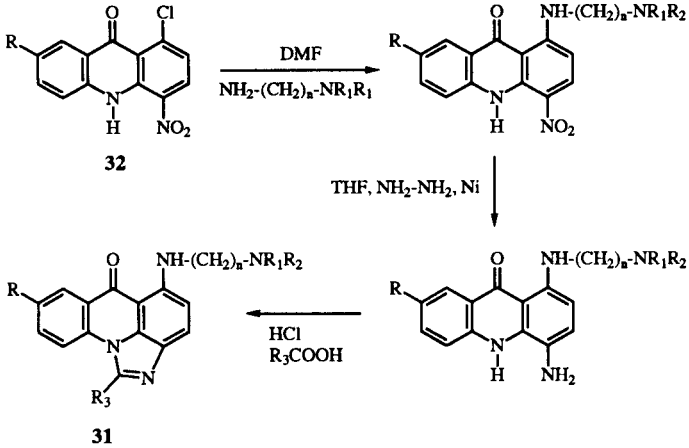


30, R = OCH_3, C_4H_9

a3. Imidazo[4,5,1-*de*]acridinone.

These derivatives **31** [n = 2,5; R = H, OH, alkoxy; R_1, R_2 = H, (substituted)alkyl, R_3 = H, alkyl] were prepared by Cholody [19-21] from 1-chloro-4-nitroacridinone **32** by amination with a suitable amine in dimethylformamide and reduction with hydrazine monohydrate in the presence of Raney nickel in tetrahydrofuran followed by cyclocondensation with carboxylic acids (Scheme 7). Their cytotoxic activity against HeLa-S_3 cells in tissue culture, their antitumor activity *in vivo* against P388 leukemia in mice and their potent cytotoxic activity against L1210 leukemia was demonstrated. Moreover, a strict relationship between the antineoplastic activity and the number of methylene spacers between proximal and distal nitrogen atoms in the side chain was established.

Scheme 7



32

31

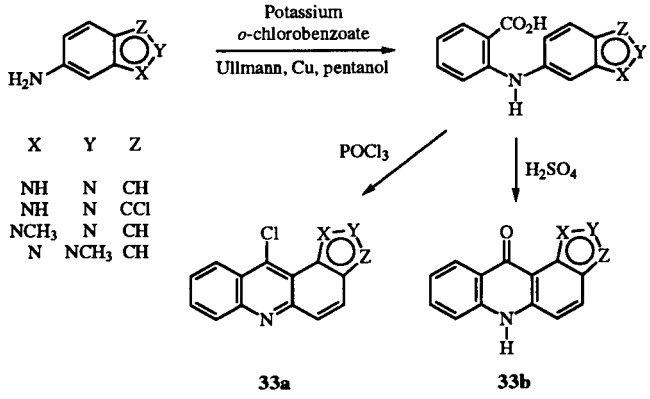
R = H, OCH_3, OH, OR'
n = 2-5
R_1, R_2 = H, C_1-C_6 alkyl, unsubstituted of substituted by OH, NH_2, *N*'-alkylamino, *N*'-*N*-dialkylamino
R_3 = H, NO_2, NH_2, C_{1-4} alkyl

b. Pyrazoloacridines.

b1. Pyrazolo[3,4-*a*]acridine.

These compounds **33** were prepared by condensing 6-aminoindazole with potassium *o*-chlorobenzoate in pentanol containing copper (Ullmann condensation, Scheme 8). The following step consisted in the cyclization by sulfuric acid or by phosphorus oxychloride: the reaction is regioselective, only the 'bent' isomer, either a 9-chloropyrazolo[3,4-*a*]acridine **33a** or a pyrazoloacridinone **33b** is obtained [22]. Nmr spectroscopy was used to establish the structure of these compounds [23].

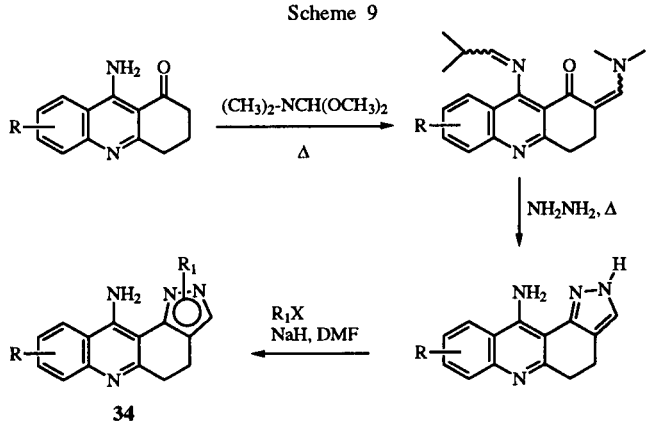
Scheme 8



33a **33b**

The synthesis of 4,5-dihydropyrazolo[3,4-*a*]acridines **34** was described in a paper and a patent by the same authors [24,25]. The reaction of 9-amino-3,4-dihydroacridinone with *N*,*N*-dimethylformamide dimethylacetal gave a reactive enaminoketone (Scheme 9), which yielded the desired heterocycle upon reaction with hydrazine. A number of substituted derivatives **34** were synthesized by alkylation of the parent heterocycle with sodium hydride and the appropriate alkyl halide. All the compounds prepared were tested as potential cholinesterase inhibitors.

Scheme 9



34

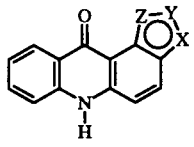
R = H, alkyl, alkoxy, halo
R_1 = H, alkyl, alkoxy, aryl, amino, aminoalkyl

b2. Pyrazolo[4,3-*a*]acridinone.

These compounds were prepared from substituted 5-aminoindazoles following the same procedure than in the case of pyrazolo[3,4-*a*]acridinones [22,23]. In this case also only the 'bent' isomer **35** was obtained.

b3. Pyrazolo[3,4-*c*]acridine.

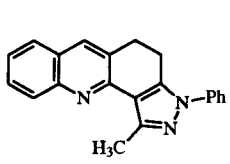
This family has only two representatives, 1-methyl-3-phenyl-4,5-dihydropyrazolo[3,4-*c*]acridine **36** [26] and



X	Y	Z
NH	N	CH
NH	N	NCl
NCH_3	N	CH
N	NCH_3	CH
NH	N	Cl

35

1-methyl-3-phenyl-1,9,9-trimethyl-4,5,8,10-tetrahydropyrazolo[3,4-*c*]acridinone **37** [27]. They were prepared by cyclocondensation of 1-phenyl-3-methyl-4-chloro-5-formyl-6,7-dihydroindazole in refluxing excess of aniline without solvent.



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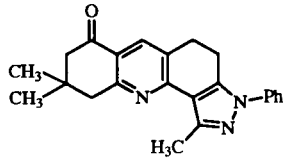


37

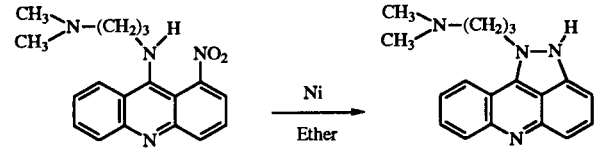
1-Methyl-3-phenyl-4,5-dihydropyrazolo[3,4-*c*]acridine **36** has been prepared by cyclocondensation of 1-phenyl-3-methyl-4-chloro-5-formyl-6,7-dihydroindazole with an excess of aniline at reflux [26].

b4. Pyrazolo[3,4,5-*kl*]acridine.

2-Aminoalkyl-5-nitropyrazolo[3,4,5-*kl*]acridinones **38** were prepared from substituted anilines *via* 1-chloro-4-nitroacridinones **32** followed by condensation with (alkylamino) alkylhydrazines [28,29]. Several pharmacological studies [30-34] proved the anticancer properties of these pyrazoloacridines against solid tumors and tumor cells resistant to other anticancer drugs. Impressive activity *in vitro* was demonstrated for the 9-hydroxy, 9-alkoxy and 9-acyloxy analogs on a L1210 leukemia line and *in vivo* against the P388 leukemia. Advanced studies led to the selection of **38** (R = 9-OMe, $R_1 = (CH_2)_3NMe_2$) for clinical trial. Moreover, compounds **38** revealed a potential anticancer drug activity against hypoxic and noncycling cells [29,30], activity against cells having the multidrug resistance phenotype [31] and solid tumor selectivity [32].

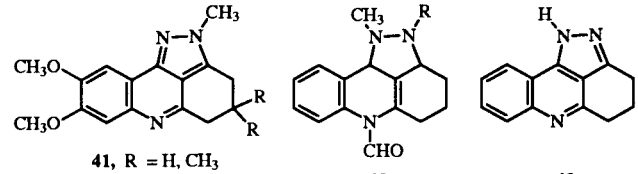
The pharmacokinetic behavior of pyrazoloacridine was evaluated in nonhuman primates. Major differences were observed in both the pharmacokinetics and toxicity between the primates and previously studied small animals. These interspecies differences may have important implications for the design of chemical trials in humans [33]. Comparative molecular field analysis (COMFA) was applied to HCT-8 and L1210 growth inhibition assays (IC50s) of a series of fourty four pyrazoloacridines with the objective of predicting improved solid tumor selectivity [34].

Reduction followed by concomitant heterocyclization of the well-known anticancer compound 'nitacrine' **39** in the presence of Raney nickel/diethylether afforded 1-dimethylaminopropylamino-2*H*-pyrazolo[3,4,5-*kl*]acridine **40** [35].



39 40

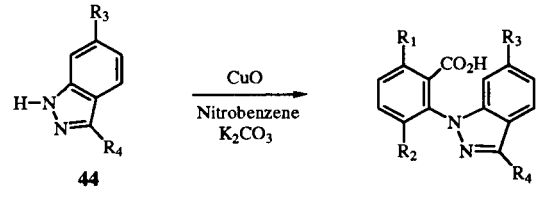
Three reduced derivatives of the same ring system **41**, **42** and **43** were described [36-38]. Compound **41** was obtained by cyclization of *p*-tolylsulfonate of 3-(3,4-dimethoxyphenyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-4-indazolone oxime in ethanol under reflux (43%). 1,3,4,5-Tetrahydropyrazolo[3,4,5-*kl*]acridine **43** was obtained as a minor product (16%) from 9-amino-3,4-dihydroacridinone subjected to the Schmidt reaction with sodium azide in sulfuric acid. This compound was prepared with the aim of studying his possible activity as acetylcholinesterase inhibitor.



41, R = H, CH_3 42 43

b5. Pyrazolo[4,5,1-*de*]acridinone.

Condensation of 3-substituted-6-nitroindazoles (R_3 = NO_2) **44** with 2-halobenzoic acids followed by a Friedel-Crafts cyclization afforded several 6*H*-pyrazolo[4,5,1-*de*]-



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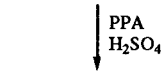
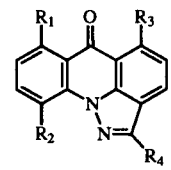


X = Br, Cl, I
R_1 = H, X, OH, OR
R_2 = OH
R_3 = H, X, NO_2, NH_2, OH, OR, NR_1R_2
R_4 = CH_2X, OH, OR, NR_1R_1



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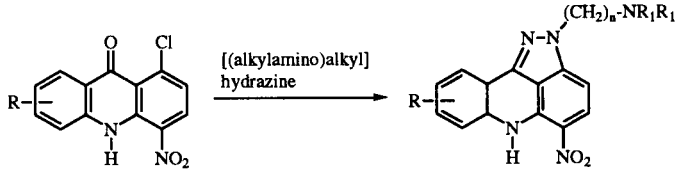


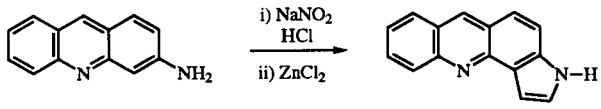
32 38

acridin-6-ones **45** [39-41]. These compounds, useful intermediates for the synthesis of antitumor agents, were prepared by a facile route from 2-halobenzoic acids and 3-substituted-6-nitroindazoles involving a halogeno copper(I)-catalyzed Ullmann coupling reaction and Friedel-Crafts cyclization. One of them was active against P388 ascites tumor in mice.

c. Pyrroloacridines.

c1. Pyrrolo[2,3-*c*]acridine.

Diazotization of 3-aminoacridine followed by reaction with methyl acetoacetate gave a mixture of *syn* and *anti* ethyl pyruvate 3-acridinylhydrazone and ethyl α-(acridinylazo)-α-acetyl propionate which was cyclized with zinc chloride [42,43] to give pyrroloacridine **46**. In these references the behavior of 3*H*-pyrrolo[2,3-*c*]acridine in electrophilic substitution reactions (Mannich, Vilsmeier, acetylation and azo coupling) was studied.



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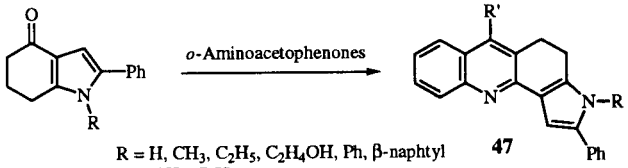
Condensation of *o*-aminoacetophenones with indolyl ketones afforded 4,5-dihydropyrrolo[2,3-*c*]acridine **47** derivatives [44].



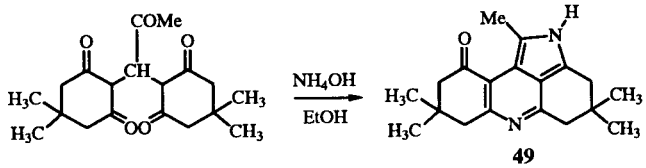
47

The synthesis of 9-amino-(3*H*)-pyrrolo[2,3-*c*]acridine **48** was achieved from proflavine in four steps [45]. Starting from proflavine, the synthesis requires protection of one of two identical exocyclic amino functions, for instance by acetylation. Monoacetylation was carried out by treating proflavine with acetic anhydride in propionic acid. Activation of the second amino group was achieved by tosylation. The reaction of the *N*-tosylated, *N'*-acetylated derivatives of proflavine with bromoacetaldehyde diethylacetal in dimethylformamide in the presence of potassium carbonate followed by intramolecular cyclocondensation gave the angular compound **48**.

48, R = Ts, H

c2. Pyrrolo[2,3,4-*kl*]acridine.

Only reduced derivatives were reported [46-50], for instance **49**. They were prepared by heating biscyclohexanediones with ammonium hydroxide in ethanol to give 86% of **49**. Pyrroloacridinones can also be obtained by treating xanthenediones with ammonia [48]. Certain octahydropyrrolo[2,3,4-*kl*]acridines showed antiradical activity (reaction with diphenylpicrylhydrazide), antioxidant properties (in methyl oleate model system) and erythrocyte-stabilizing activities; moreover, they inactivated singlet oxygen [49,50].



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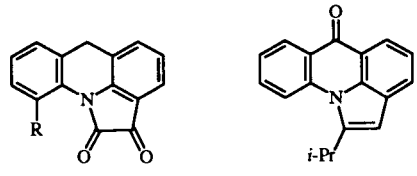
c3. Pyrrolo[3,2,1-*de*]acridine.

4,5-Dihydro-3*H*-pyrrolo[3,2,1-*de*]acridine-1,2-dione was prepared in 1938 [51,52]. Treatment of acridan or 4-carbomethoxyacridan with oxalyl chloride followed by reaction with aluminium chloride led to the isatin analog of acridan **50** in 88% or 52% yield respectively. 6*H*-pyrrolo[3,2,1-*de*]acridinan-1,2-dione **50** can be used to produce, by a new route, 4-substituted and 4,5-disubstituted acridans [53].



50, R = H, CO_2CH_3 **51**

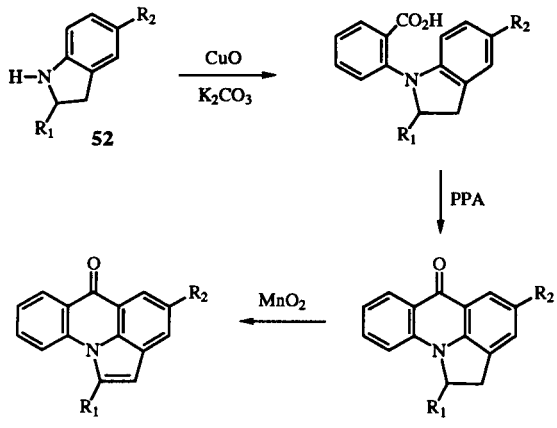
Another method to prepare pyrrolo[3,2,1-*de*]acridinone **51** (yield 10%) consisted in the reaction between 9-acridinone and 3-chloro-3-methyl-1-butyne during 72 hours at reflux in phase transfer catalysis conditions [54].

Finally, these compounds can also be prepared using the Ullmann reaction: indolylbenzoates (R_1 = H, Me; R_2 = H, MeO) were obtained in 40-92% yield by reaction of 5-substituted-2-chlorobenzoic acid with a substituted indoline **52** in the presence of potassium carbonate and cupric oxide, followed by cyclization of the indolylbenzoate with polyphosphoric acid to give 10-90% of pyrroloacridinones. Treatment of pyrroloacridinones with manganese dioxide gave pyrroloacridinones **53** in 75-78% yield [55] (Scheme 10).

4. Tetracyclic Oxygen Acridines. Alkaloids.

Due to their pharmacological interest, these compounds were widely studied: reviews on syntheses, new natural sources, metabolism and action mechanism as

Scheme 10



52

53

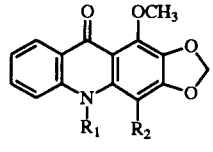
R_1 = H, CH_3
R_2 = H, CH_3

well as toxicology were published. We will summarize here only the most relevant aspects. A review reports all acridine alkaloids both natural and synthetic [56].

a. Dioxoloacridines.

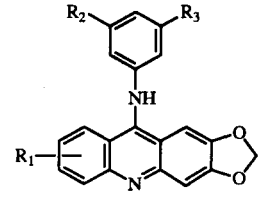
a1. Dioxolo[4,5-*b*]acridine.

Many alkaloids belong to this family. The constitution of the alkaloids evoxanthidine **54**, evoxanthine **55**, xanthevodine **56** and melicopidine **57**, isolated from many species of *Rutaceae* [60-62] were confirmed by total synthesis. Dallacker and Adolphen synthesized for the first time these dioxoloacridines [57,58]. Anthranilic acid and 2,5-dimethoxy-3,4-methylenedioxyiodobenzene heated in isoamyl alcohol in the presence of copper afforded 2,5-dimethoxy-3,4-methylenedioxy-2'-carboxydiphenylamine which was subsequently cyclized by the action of phosphorus oxychloride to 1,4-dimethoxy-2,3-methylenedioxy-9-chloroacridine. Further treatment with 2*N* hydrochloric acid at 100° gave **56**, which was methylated with methyl iodide-potassium hydroxide in acetone to give **57**. Analogously, evoxanthine and evoxanthidine were obtained from anthranilic acid and 3-methoxy-4,5-methylenedioxy-iodobenzene. All have 'linear' structures which were established spectroscopically [59].



54, R_1 = H, R_2 = H (Evoxantidine)
55, R_1 = CH_3, R_2 = H (Evoxanthine)
56, R_1 = H, R_2 = OCH_3 (Xanthevodine)
57, R_1 = CH_3, R_2 = OCH_3 (Melicopidine)

Kimura [63] prepared twelve novel 9-anilino-2,3-methylenedioxyacridines **58** and evaluated their activity against L1210 leukemia *in vivo*. Compounds **58** were prepared in several steps starting by the condensation of 2-chloro-4,5-methylenedioxybenzoic acid with aniline to give 2-anilino-4,5-methylenedioxybenzoic acid. These compounds were cyclized using phosphorus oxychloride to yield 9-chloro-2,3-methylenedioxyacridines which were aminated with methanesulfonyl-*m*-anisidine to give the derivatives **58**. Some of them possessed the same potency of the antitumor activity as amsacrine, which is an important antitumor agent in clinical use. The molecular structure of **58** (R_1 = H, R_3 = MeO, R_4 = $NHSO_2Me$) was determined by single-crystal X-ray diffraction which proved that the methylenedioxy group in **58** is fused at the 2- and 3-positions of the acridine ring.

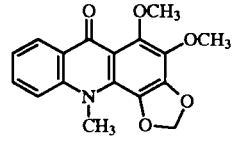


58

R_1 = H, CH_3, Cl, CH_3O
R_2 = CH_3O, H
R_3 = H, CH_3, $NHSO_2CH_3$

a2. Dioxolo[4,5-*c*]acridine.

Adolphen and Dallacker [57] synthesized the alkaloid melicopine **59** from 2,3-methylenedioxy-4,5-dimethoxy-iodobenzene and anthranilic acid.



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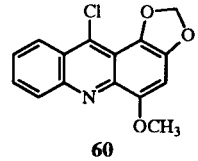
a3. Dioxolo[4,5-*a*]acridine.

Analogously, the same authors prepared compound **60** by cyclization of 4,5-methylenedioxy-2'-carboxydiphenylamine with phosphorous oxychloride [64].



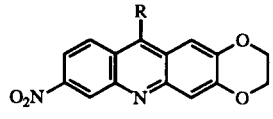
60

b. Dioxinoacridines.

b1. Dioxino[2,3-*b*]acridine.

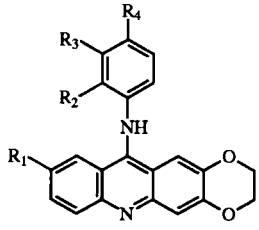
A publication [65] and three patents [66-68] concerned this family of compounds which have always had a nitro group at position 8. The condensation of 6-nitro-1,4-benzodioxane with 2-chloro-4-nitrobenzoic acid, followed

by cyclization in the presence of phosphorus oxychloride gave compound **61**. From compound **61**, (R = Cl, 'linear' structure), derivatives **62** and **63** were prepared by reaction of hydroxyalkylamines or by hydroxyalkylaminoalkylamines in phenol. These compounds have an antirickettsial activity.



61, R = Cl
62, R = NH-$(CH_2)_n$-CH_2OH (n = 1-5)
63, R = NH-$(CH_2)_n$-NH-$(CH_2)_n$-CH_2OH (n = 2-8)

9-Anilino-2,3-ethylenedioxyacridines were prepared by Kimura [69]. The anticancer activity of compounds **64a** and **64b** was similar to that of amsacrine. Compounds **64** were prepared by condensation of 6-amino-1,4-benzodioxane with 2-chlorobenzoic acid followed first by cyclization using phosphorus oxychloride, then coupled with the appropriate arylamines bearing CH_3O, $NHSO_2CH_3$ or CH_3 groups as side chains to provide the desired new types of 9-anilinoacridines. The reaction was carried out 'one-pot' and only the 'linear' isomer was isolated. These derivatives were prepared to be evaluated for activity against P 388 leukemia *in vivo*. Some of them possessed the same potency of antitumor activity as amsacrine.

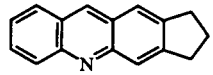


64a, R_1, R_2, R_3 = H, CH_3O, H, R_4 = $NHSO_2Me$
64b, R_1, R_2, R_3 = Cl, H, H, R_4 = $NHSO_2Me$
64c, R_1, R_2, R_3, R_4 = H, H, CH_3, $NHSO_2Me$
64d, R_1, R_2, R_4 = H, R_3 = $NHSO_2Me$
64e, R_1, R_2, R_3, R_4 = H

5. Tetracyclic Carbocyclic Acridines.

a. Cyclopent[*b*]acridine.

There is only one representative of this family, cyclopent[*b*]acridine **65** [70] which was prepared in 83% yield by cyclization, in the presence of sulfuric acid, of *N*-(indan-5-yl)anthranilic acid followed by sodium reduction.



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