THIAZOLOBENZIMIDAZOLES

Alba Chimirri, Silvana Grasso, Giovanni Romeo, and Maria Zappala
Dipartimento Farmaco-Chimico - Universita - Viale SS. Annunziata,
98100 Messina, Italy

Abstract - This review describes the synthesis, the reactivity, the spectroscopic data and the biological activities of thiazolobenzimidazoles.

CONTENTS:
I. Introduction
II. Synthetic approaches to thiazolobenzimidazoles
   A. Synthesis of thiazolo[3,2-a]benzimidazoles
   B. Synthesis of thiazolo[3,2-a]benzimidazol-3(2H)-ones
   C. Synthesis of thiazolo[3,4-a]benzimidazoles
   D. Synthesis of thiazolo[3,2-c]benzimidazoles
III. Reactions of thiazolobenzimidazoles
IV. Spectroscopy
V. Biological activity
References

I. INTRODUCTION
The interesting biological activities of thiazolobenzimidazoles have stimulated the exploitation of the chemistry of this class of compounds and an enormous number of papers and patents have appeared in literature. Three fundamental thiazolobenzimidazole systems have been reported, which show different fusion of the sulfur containing ring to the edges of benzimidazole moiety. This article appears to be the first survey of the chemistry and biological activity of this important group of heterocyclic compounds.
II SYNTHETIC APPROACHES TO THIAZOLOBENZIMIDAZOLES

A. SYNTHESIS OF THIAZOL[3,2-a]BENZIMIDAZOLES

1. By reaction of 2-mercaptobenzimidazoles with α-halocarbonyl compounds.

Thiazolo[3,2-a]benzimidazoles have received intensive study and several synthetic routes have appeared in literature. The earliest approach to thiazolo[3,2-a]benzimidazole system was reported in 1937 by Andersag and Westphall. A synthetic route was described to 3-methylthiazolo[3,2-a]benzimidazole, which involved the cyclization of 2-mercaptobenzimidazole with chloroacetone and sodium in ethyl alcohol.

Later, the same reaction was extended to the preparation of numerous thiazolo[3,2-a]benzimidazoles (3) by condensation of 2-mercaptobenzimidazoles (1) with various α-halocarbonyl compounds, through formation of acyclic intermediates (2) which promptly cyclized to (3). The formation of 2,3-dihydro-3-hydroxythiazolo[3,2-a]benzimidazole as intermediate in the cyclization process have been also reported. Treatment of compounds (3) with alkyl or aryl halides gave 9-substituted thiazolo[3,2-a]benzimidazolium salts.

![Diagram](attachment:image.png)

Similarly, by treatment of 2-mercaptobenzimidazoles (1) with p-R'\text{C}_6\text{H}_4\text{COCHBrCH}_2\text{CO}_2\text{R}' followed by successive cyclization, 3-aryl-2,3-dihydro-3-hydroxythiazolo[3,2-a]benzimidol-2-acetic acid derivatives (4) were prepared, which, by dehydration in HCl and dioxane, afforded 3-aryltiazolo[3,2-a]benzimidazol-2-acetic acid derivatives (5).

![Diagram](attachment:image.png)
2. By reaction of 2-mercaptobenzimidazoles with α-haloacetals.

A strictly related route to thiazolo[3,2-a]benzimidazoles was envisaged\textsuperscript{6,9,32,33} by using α-haloacetals as starting material. 2-Mercaptobenzimidazoles (1) were condensed with α-haloacetals to give 2,3-dihydro-3-hydroxythiazolo[3,2-a] benzimidazoles (6) which, by intramolecular dehydration in acidic medium, afforded thiazolo[3,2-a]benzimidazoles (8). In some cases\textsuperscript{32,33}, isolation of acetals of benzimidazole-2-mercaptocarboxaldehyde (7), as possible intermediates of the process, has been reported; 7 underwent cyclization to the same compounds (8).

\[ \text{\textsuperscript{X}} \text{Cl, Br} \\
\text{R} = \text{H, Me, Ph} \\
\text{R}^1 = \text{H, Me} \\
\text{R}^2 = \text{H, Me} \]

3. By reaction of 2-mercaptobenzimidazoles with propargyl halides.

A different kind of approach to thiazolo[3,2-a]benzimidazole derivatives involved the cyclization of 2-mercaptobenzimidazole derivatives (1) with propargyl halides\textsuperscript{15,34-38}. The obtained 2-(2-propynylthio)benzimidazoles·HBr (9) could be converted, by heating in Na/\text{EtOH}\textsuperscript{15,34-36}, or in \text{AcOH}/\text{Hg(OAc)}\textsuperscript{2}\textsuperscript{36}, into 3-substituted thiazolo[3,2-a]benzimidazoles (10). The same intermediates 9, heated in (\text{Me}_2\text{N})_3\text{PO}\textsuperscript{37} afforded, after 3,3-sigmatropic Claisen rearrangement, a mixture of 2-substituted thiazolo[3,2-a]benzimidazoles (11 and 12); treatment of 9 with \text{Et}_3\text{N}/\text{EtOH}\textsuperscript{38} gave 2,3-dihydro-3-methylenethiazolo[3,2-a]benzimidazole (13, R=H). Reaction mechanisms for the cyclization of propargylammonium halide derivatives were discussed\textsuperscript{34}. 

--- 1977 ---
4. By reaction of 2-mercaptobenzimidazoles with 1,2-dihaloethyl derivatives

The synthetic route which utilizes vicinal dihalides to promote the cyclization to 2,3-dihydrothiazolo[3,2-a]benzimidazoles (15) has been also exploited. The approach is based on the condensation of 1 with dihaloethyl derivatives in the presence of basic reagents, followed by cyclization of the obtained 2-(6-haloethylthio)benzimidazoles (14). If ethylene halohydrins were used, 2-(8-hydroxyethylthio)benzimidazoles (14, X=OH) were obtained as intermediates which, by reaction with SOCl₂, gave the corresponding chloroderivatives (15) (X=Cl); further cyclization afforded 15.
5. By reaction of 2-mercaptobenzimidazoles with other reagents.

By reaction of 2-mercaptobenzimidazole (1) with \( \text{F}_3\text{C}N=\text{CF}-\text{CF}=\text{NFCF}_3 \) or with hexafluorobut-2-ynyl \( \text{2H,3H-2,3-bis(trifluoromethylimino)thiazolo[3,2-a]benzimidazole (16) and 2,3-bis(trifluoromethyl)thiazolo[3,2-a]benzimidazole (17) were obtained respectively.} \)

![Chemical structure of 16 and 17](image)

Treatment of 1 with arylhydrazones of ethyl \( \gamma\)-bromo-\( \alpha,\beta\)-dioxbutyrate afforded\(^5\) \( \text{thiazolo[3,2-a]benzimidazoles (18), whereas reaction of 1 with 1-bromo-2,3-epoxy-3-methylbutane gave} \) \( \text{2,3-dihydro-3-[(1-hydroxyisopropyl)thiazolo[3,2-a]benzimidazole (19) and 3-hydroxy-4,4-dimethylthiazolo[3,2-a]benzimidazole (20).} \)

![Chemical structure of 18, 19, and 20](image)

Only one example of synthesis which starts from 1-substituted 2-mercaptobenzimidazole was reported\(^5\); the reaction with \( \alpha\)-bromophenylacetic acid gave the 2-phenyl-3-hydroxythiazolo[3,2-a]benzimidazol-4-ium salt.

A German group\(^5\) prepared 3-phenylthiazolo[3,2-a]benzimidazoles (22) by treatment of 2-mercaptobenzimidazoles (1) with mercury bis(phenylacetylide) and aryl isocyanates. A mechanism was postulated which involved the formation of a dithiazepine (21) and the successive transformation in 22 by elimination of aryl isocyanates.
6. From 1-(β-hydroxyethyl)-2-mercaptobenzimidazoles.

2,3-Dihydrothiazolo[3,2-a]benzimidazoles (25) were also prepared by cyclization of the 1-(β-hydroxyethyl)-2-mercaptobenzimidazoles (24)58-60 with SOCl₂ or POCl₃. Compounds 24 can be synthesized by boiling in alcoholic KOH a mixture of N-(β-hydroxyethyl)-2-aminoanilines (23) with CS₂58, by heating a MeOH solution of 2-chloro-1-hydroxyethylbenzimidazoles (26) with thiourea59-60 or by reduction of 1-acylmethyl-2-mercaptobenzimidazoles (27) with NaBH₄60. The intramolecular cyclization of 27 with POCl₃ led to thiazolo[3,2-a]benzimidazoles (28)61-63.

R = H, Me, NO₂, NH₂, NHAc at position 6 or 7
R¹ = H, alkyl, phenyl, ary1, 2-naphthyl, 2-thienyl

--- 1980 ---
7. From 2-acyl- or 2-cyanomethylthiobenzimidazoles.

By a single step reaction of 2-acylmethylthiobenzimidazoles (29) with carboxylic acid anhydrides in the presence of the corresponding sodium salts, 2-acylthiazolo[3,2-a]benzimidazoles (30) were obtained.

\[
\begin{align*}
\text{R} & = \text{CO}_2\text{Ph, CO}_2\text{Et, acyl} \\
\text{R}' & = \text{Me, Et, Ph} \\
\text{R}'' & = \text{OH, alkyl}
\end{align*}
\]

Reaction of cyanomethylthiobenzimidazole (31) with dimethyl acetylenedicarboxylate gave thiazolo[3,2-a]benzimidazole derivative (32) which could be also obtained from benzimidazo[1,2-d][1,2,4]thiadiazol-3(2H)-one (33). At 90°C with malononitrile, compound 33 afforded the imino derivative 34 with elimination of isocyanate.

8. By reaction of p-benzoquinone with 2-aminothiazoles.

A particular method to obtain 6-hydroxythiazolo[3,2-a]benzimidazoles (35) was described by reaction of p-benzoquinone with 2-aminothiazoles in acetic acid.

\[
\begin{align*}
\text{R} & = \text{Me, Ph, aryl, 2-naphthyl, 2-thienyl} \\
\text{R}' & = \text{H, CO}_2\text{Et, Me, Ph}
\end{align*}
\]

— 1981 —

1-(2-Thiazoly]benzotriazole (36) gave 73-74% of thiazolo[3,2-a]benzimidazole (37) on photolysis and 10% on acid catalyzed thermolysis along with noncyclic water soluble compounds. Compound 37 was obtained by elimination of N₂ from the benzotriazoly] group and selective ring closure on the nitrogen of the heterocyclic substituent. The photolysis and the thermolysis were thought to involve different mechanisms.

B. SYNTHESIS OF THIAZOLO[3,2-a]BENZIMIDAZOL-3(2H)-ONES

1. By reaction of 2-mercaptobenzimidazoles with chloroacetic acid and related compounds.

Condensation of 2-mercaptobenzimidazoles [1] in methanol or ethanol with an equimolecular amount of chloroacetic acid (or its sodium salt) in the presence of AcONa afforded (2-benzimidazoly]thioacetic acid (38) which, under various cyclization conditions, such as Dowtherm A, Ac₂O/Py or dicyclohexylcarbodimide/Py, gave thiazolo[3,2-a]benzimidazol-3(2H)-ones (39). The cyclization of 5-substituted 38 led to the formation of two isomers with the substituent in 6 or 7 position, as established through nmr analysis of the reaction products. The cyclization of derivatives 38, performed in the presence of aromatic aldehydes, gave 2-benzylidene derivatives in good yields. These compounds have also been obtained by directly refluxing 2-mercaptobenzimidazole 1 with an equimolecular amount of chloroacetic acid and aromatic aldehydes.

R = H, Br, Cl, CO₂Me, COPh, Me, NO₂, OMe at various positions
Similarly, the reaction between 1,2-dihydro-2-mercaptobenzimidazole and chloroacetic acid afforded \(^9\) \(^8\) \(9,9\alpha\)-dihydrothiazolo[3,2-a]benzimidazol-3(2H)-one (40).

![Chemical structure of 40](image)

\(2-\alpha\)-Hydroxyethylidene)thiazolo[3,2-a]benzimidazol-3(2H)-one acetate ester (42) was prepared \(^9\) \(^9\) by refluxing in \(Ac_2O\) the appropriate \(2\)-benzimidazolylthio)acetic acid (41).

![Chemical structures of 41 and 42](image)

\(2\)-Arylhydrazone-thiazolo[3,2-a]benzimidazol-3(2H)-ones (43) were synthesized \(^1\) \(^8\) \(^0\) \(^0\) - \(^2\) in one step by treating 2-mercaptobenzimidazole (1) with arylazochloroacetyl chloride in an organic solvent, e.g. a mixture of dioxane and benzene, in the presence of a HCl acceptor as \(Et_3N\).

Under similar experimental conditions, 1 reacted with phenyliminochloroacetyl chloride to give \(^1\) \(^0\) \(^1\), \(^1\) \(^3\) \(2\)-(phenylimino)thiazolo[3,2-a]benzimidazol-3(2H)-one (44).
2. By reaction of 2-mercaptobenzimidazoles with acetylenedicarboxylate.

The reaction between 1 and dimethyl or diethyl acetylenedicarboxylate in acetic acid or methanol, which in earliest papers\textsuperscript{104,105} was claimed to give the thiazolo-
benzimidazole \textbf{45} as unique polycyclic compound, has been successively investigated. In fact, it has been pointed out\textsuperscript{106,107} that an isomeric compound can also be obtained to which structure \textbf{46} was assigned. Finally, the reaction pathway has been fully elucidated: 2-mercaptobenzimidazole and dimethyl acetylenedicarboxylate react in wet or dry acetonitrile to give only \textbf{45}, while in dry methanol \textbf{46} is the only isolated product. It has been shown that adduct \textbf{45} can be converted\textsuperscript{108,109} into \textbf{46} by refluxing in dry methanol; this rearrangement is catalyzed by basic impurities (e.g. MeONa), so it does not occur in methanol containing catalytic amounts of acetic acid. Structure \textbf{45} was confirmed\textsuperscript{106} by X-ray crystallographic analysis and by its preparation from \textbf{1} via condensation with maleic anhydride followed by successive methylation with CH\textsubscript{2}N\textsubscript{2} in THF, bromination in AcOH and dehydrobromination in alkaline solution.

\begin{center}
\begin{tikzpicture}
\node [align=center] at (0,0) {\textbf{45} \quad \textbf{46}};
\end{tikzpicture}
\end{center}

\textbf{R} = Me, Et

3. By reaction of 2-mercaptobenzimidazoles with other bifunctional reagents.

Treatment of 2-mercaptobenzimidazoles \textbf{(1)} with hexafluoro-1,2-epoxypropane\textsuperscript{110} or with maleic anhydride\textsuperscript{106,111,112} gave 2-substituted thiazolo[3,2-a]benzimidazol-3(2H)-ones \textbf{47} and \textbf{48} respectively.

\begin{center}
\begin{tikzpicture}
\node [align=center] at (0,0) {\textbf{47} \quad \textbf{48}};
\end{tikzpicture}
\end{center}

When \textbf{1} was treated with 2-chlorohydroxamoyl chloride\textsuperscript{113,114}, thiazolo[3,2-a]benzimidazol-3-oxime (\textbf{49}) was obtained which, by reaction with MeCNO gave the corresponding 0-methylaminocarbonyl derivative.
C. SYNTHESIS OF THIAZOLO[3,4-a]BENZIMIDAZOLES

Only few papers concerning the chemistry and the biological activity of thiazolo-[3,4-a]benzimidazoles have appeared. The cyclocondensation of suitable substituted benzimidazoles (50) with sulfur containing compounds is the most general synthetic approach.

By reaction of 2-(chloromethyl)benzimidazoles (50) with ammonium thiocyanate in methanol 1-imino-1H,3H-thiazolo[3,4-a]benzimidazoles (51) were obtained, which by treatment with conc. HCl gave 1H,3H-thiazolo[3,4-a]benzimidazol-1-ones (52).

Compound 51 have been also synthesized by intramolecular cyclization of 2-(thiocyanatoalkyl)benzimidazoles.

\[
\begin{align*}
R = H, Me, (un)substituted benzylidene, thiényliden, furfuryliden \\
R^{1} = H, Me; R^{2} = H, Cl, Me
\end{align*}
\]

By cyclization of 1,2-dibenzoylbenzimidazole (53) with P₂S₅, 1,3-diphenylthiazolo-[3,4-a]benzimidazole (54), a new 10π-electron heterocycle containing tetravalent sulfur, was prepared.

Recently, a novel one pot synthesis of 1H,3H-thiazolo[3,4-a]benzimidazoles (56) has been developed by the authors of the present review, starting from very simple and easily available precursors. o-Phenylenediamine (55) was made to react with a variety of carbonyl compounds in an excess of 2-mercaptocarboxylic acids: compounds 56 were obtained in good yields. The spectral data (¹H-nmr and ms) of the synthesized compounds were also reported.

\[
\begin{align*}
R = \text{alkyl, phenyl} \\
R^{1} = H, Me, Et; R^{2} = H, Me
\end{align*}
\]
D. SYNTHESIS OF THIAZOLO[3,2-c]BENZIMIDAZOLES

Only one example of synthetic approach to thiazolo[3,2-c]benzimidazole system was reported. Cycloaddition of 5-aryl-3-methylimidazo[5,1-b]thiazoles (57) with dialkyl acetylenedicarboxylate in an aprotic solvent gave a number of products including epimeric thiazolo[3,2-c]benzimidazoles (58).

\[ \text{Thiazolo[3,2-c]benzimidazoles} \]

III REACTIONS OF THIAZOLOBENZIMIDAZOLES

Very little data concerning the reactivity of thiazolo[3,2-a] and [3,4-a]benzimidazoles have been published. On the contrary, numerous reports deal with the chemical behaviour of thiazolo[3,2-a]benzimidazol-3(2H)-ones owing to the mobility of methylene protons adjacent to the carbonyl group.

In a study on the thiocyanation and bromination of heterocyclic compounds, Kano reported that thiocyanation of thiazolo[3,2-a]benzimidazole derivatives (59) did not proceed, whereas 2-bromo derivatives can be obtained in good yields by bromine in CHCl₃ solution. Bromination of analogous substrates (59) with N-bromosuccinimide led to 2-bromo- and 2,8-dibromothiazolo[3,2-a]benzimidazoles.

Compound (59; R'=R₂=H, R=Me) was allowed to react with a cepham derivative to give thiazolo[3,2-a]benzimidazolium 9-cephem substituted (60).

\[ \text{Reactions of thiazolo[3,2-a]benzimidazoles} \]

R = Me, Et

R₂ = Me, Ph, p-Cl-, p-BrPh
R₁ = H, Br
R₂ = H, Me

Cycloaddition of 3-methylthiazolo[3,2-a]benzimidazole (61) with dimethyl acetylenedicarboxylate followed dual courses depending on the polarity of the
solvent. With an aprotic non polar solvent, pyrrolo[2,1-b]thiazole (62) was obtained, while the formation of pyrido[1,2-a]benzimidazole (63) was observed in an aprotic polar solvent. The same compound reacted with methyl propiolate in MeCN to give \(^{128}\) a thiazolo[3,2-a][1,5]benzodiazepine (64): the reaction mechanism involved a dipolar cycloaddition followed by a ring-enlargement.

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} & \quad \text{Me} \\
\text{S} & \quad \text{N} & \quad \text{S} \\
\text{N} & \quad \text{S} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{HC=CCO}_2\text{Me} & \quad \text{CCO}_2\text{Me} & \quad \text{CCO}_2\text{Me} \\
\text{Me} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

2,3-Dihydrothiazolo[3,2-a]benzimidazoles (65) by oxidation gave \(^{49}\) S-oxide derivatives, whereas the oxidation of the analogous 3-hydroxy derivative (R=H, R'=OH) afforded \(^{5}\) thiazolo[3,2-a]benzimidazol-3(2H)-one. Tautomerism of the 2,3-dihydro-3-hydroxythiazolo[3,2-a]benzimidazoles was also investigated. Compounds 65 (R=H, R'=Me, OH) underwent nitrogen acetylation and rearrangement under acetylation conditions \(^{5}\).

\[
\begin{align*}
\text{R} = \text{H}, \text{Ph}, \text{Py} \\
\text{R'} = \text{H}, \text{Me}, \text{OH}
\end{align*}
\]

The mobility of the protons of the methylene group at position 2 in the thiazolo-[3,2-a]benzimidazol-3(2H)-one derivatives was evidenced by the reaction with aryl diazonium salts, nitroso compounds and aromatic aldehydes.
Thus, treatment with ArNO$_2$-80-82,85,95 and ArN$_2$X-80,81,85,92,95,129,130 afforded imino-66 and diazo derivatives 67 respectively.

When treated with Grignard reagents 2-arylazothiazolo[3,2-a]benzimidazol-3(2H)-ones 67 underwent opening of the thiazole ring to give 2-(1-arylazo-2,2-diaryl-2-hydroxyethylmercapto)benzimidazoles 68, whereas imino derivatives 66 showed addition to the carbonyl group in the same experimental conditions.

$$\text{R} = \text{Ph, p-MePh, PhCH}_2$$

Compound 67 (R=H) was also reduced with sodium hydrosulfite and the resulting amine was treated with aryl isocyanates to give 2-(2-thio-3-arylureido)thiazolo[3,2-a]-benzimidazol-3(2H)-ones 69.

The electrochemical reduction and oxidation of a series of 2-arylothiazolo-[3,2-a]benzimidazol-3(2H)-ones were also examined and the obtained products were isolated and identified.

By refluxing thiazolo[3,2-a]benzimidazol-3(2H)-ones (70) with suitable aromatic aldehydes in Py/dicyclohexylcarbodiimide or in AcOH/AcONa, 2-arylidene-thiazolo-[3,2-a]benzimidazol-3(2H)-ones (71) were obtained. Some 2,α-dibromoderivatives were also prepared by addition of bromine to the exocyclic double bond.
In a similar way, reaction of $\text{70 (R=H)}$ with acetone in EtOH in the presence of piperidine gave the corresponding 2-isopropylidene derivative.$\text{78}$

\[
\begin{array}{c}
\text{N} \begin{array}{c} \text{S} \\ \text{CHR} \end{array} \text{N} \begin{array}{c} \text{S} \\ \text{CH} \end{array} \\
\text{70} \\
\end{array}
\begin{array}{c}
\text{RCHO} \\
\end{array}
\begin{array}{c}
\text{N} \begin{array}{c} \text{S} \\ \text{CH} \end{array} \\
\text{71} \\
\end{array}
\]

$R = \text{Phenyl, aryl, heteroaryl}$

Condensation reaction$\text{139}$ of $\text{70 (R=H)}$ with 2-nitrobenzaldehyde, followed by reductive cyclization, afforded quinolino[3,2:5',4']thiazolo[3',2'-a]benzimidazole ($\text{72}$).

\[
\text{72}
\]

Polarographic reduction$\text{140}$ and anodic oxidation$\text{133}$ of some 2-arylidene thiazolo[3,2-a]benzimidazol-3(2H)-ones were also investigated. Hydrolysis of derivatives $\text{71}$ both in acidic and alkaline medium afforded 5-arylidene derivatives of 3-(o-aminophenyl)thiazolidine-2,4-dione ($\text{73}$)$\text{79,96}$ and $\alpha$-(2-benzimidazolylthio)-8-arylacrylic acids ($\text{74}$)$\text{94}$ respectively. Analogously, compounds $\text{70}$ treated with HCl gave$\text{78}$ 3-(o-aminophenyl)thiazolidine-2,4-dione; 2-(2-benzimidazolylthio)succinic acid ($\text{75}$) was obtained$\text{141}$ from alkaline (NaOH) treatment of thiazolo[3,2-a]benzimidazol-3(2H)-one-2-acetic acid.

By action of amines on thiazolo[3,2-a]benzimidazol-3(2H)-one ($\text{70}$), amides of (2-benzimidazolylthio)acetic acid ($\text{76}$) were available$\text{131}$.

\[
\begin{array}{c}
\text{N} \begin{array}{c} \text{S} \\ \text{CH} \end{array} \\
\text{Ar} \\
\text{73} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} \begin{array}{c} \text{S} \\ \text{CH} \end{array} \\
\text{Ar} \begin{array}{c} \text{COOH} \\
\text{74} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} \begin{array}{c} \text{S} \\ \text{CHCOOH} \\
\text{75} \\
\end{array} \\
\text{76} \begin{array}{c} \text{CONHR} \\
\end{array} \\
\end{array}
\]

$R = \text{alkyl, aryl}$
Cyclocondensation\textsuperscript{142} of some 2-arylidenethiazolo[3,2-a]benzimidazol-3(2H)-ones (71) with malononitrile, ethyl cyanoacetate and cyanoacetamide afforded pyrano and pyrido[2,3:4',5']thiazolo[3,2-a]benzimidazole derivatives (77).

![Diagram 77]

\[ X = O, N \]

Grignard reagents added to the exocyclic C=C bond in 2-arylidene derivatives 71 to give\textsuperscript{131} the corresponding 2-(\(a\)-alkyl) and 2-(\(a\)-aryl)benzylthiazolo[3,2-a]benzimidazol-3(2H)-ones. Furthermore, compounds 71 reacted with diazomethane\textsuperscript{131} to give the corresponding \(a\)-methyl derivatives. Mannich bases 78 were prepared\textsuperscript{83} in good yields from thiazolo[3,2-a]benzimidazol-3(2H)-one (70).

![Diagram 78]

\[ R = R' = \text{alkyl, phenyl} \]

By heating with disubstituted formamides and POCl\textsubscript{3}, 70 gave \(N,N\)-disubstituted aminomethylene derivatives 79\textsuperscript{143,144}. These compounds could be also obtained by reaction of 2-ethoxymethylenethiazolo[3,2-a]benzimidazol-3(2H)-one (80) with primary amines\textsuperscript{145}. Successive reaction of 79 with POCl\textsubscript{3} afforded\textsuperscript{144} 3-chlorothiazolo-[3,2-a]benzimidazole-2-carboxaldehyde (81).

![Diagram 79 and 81]

\[ R = R' = H, Me; R^2 = \text{Me, NH}_2, \text{CH}_2\text{CH}_2\text{OH, CH}_2\text{COOH, Ph, p-NO}_2\text{Ph} \]
Merocyanine dyes (82) were prepared by heating, in the presence of a carboxylic acid anhydride and a tertiary base, thiazolo[3,2-a]benzimidazol-3(2H)-one (70)[77,146-151] or (2-benzimidazolylthio)acetic acid[152] with a quaternary salt of a five- or six-membered mono or bicyclic hetero-compounds containing a reactive thioether or vinyl group in α-position.

\[
\begin{align*}
\text{R} &= \text{MeS, EtS, PhNH, PhN-; } R' = \text{Me, Et; } n = 0, 1, 2 \\
Z &= \text{residue of imidazole, pyrrole, thiazole, benzimidazole, indole, benzothiazole, benzoazole, quinoline.}
\end{align*}
\]

Similarly[151] 70 was condensed with its acetanilidomethylene (n=0) or acetanilidoallylidene (n=1) derivatives (83) (as quaternary salts) to give dyes 84.

\[
\begin{align*}
\text{R} &= \text{CH-(CH=CH)}_n\text{N-Ph} \\
n &= 0, 1
\end{align*}
\]

Another route to merocyanine derivatives proceeded[77,153-157] via 2-ethoxymethylene-thiazolo[3,2-a]benzimidazol-3(2H)-one (80) with 1-methyl substituted nitrogen heterocycles. Compound 80 was obtained by reaction of 70 with ethyl orthoformate[77,136,145,153-157].

\[
\begin{align*}
Z &= \text{nitrogen containing heterocyclic residue, such as imidazole, thiazole, tetrazole, triazole, benzothiazole, pyrazole.}
\end{align*}
\]

Z = nitrogen containing heterocyclic residue, such as imidazole, thiazole, tetrazole, triazole, benzothiazole, pyrazole.
It was reported that the condensation reaction between 2-[(1,5,5-trimethyl-4-methylthio)-3-imidazolyl-2-ylidene]thiazolo[3,2-a]benzimidazol-3(2H)-one (86) and ethiodide of quinaidine or ethiodide of 2-methylbenzothiazole gave the dye 87.

\[
\begin{align*}
\text{Z} &= \text{residue of quinoline, benzothiazole.}
\end{align*}
\]

All the above mentioned merocyanine dyes and other correlated compounds are useful as photographic sensitizers for silver halide emulsions. Few data on the reactivity of thiazolo[3,4-a]benzimidazoles concerned the 3-imino derivatives; reaction with isocyanates and acyl anhydrides afforded thiazolobenzimidazolylideneureas (88) and thiazolobenzimidazolylideneamides (89) respectively.

A cycloaddition reaction with alkenes and alkynes was reported for 1,3-diphenylthiazolo[3,4-a]benzimidazole (54) containing tetravalent sulfur, which occurred across the thiocarbonyl ylide dipole in highly stereoselective and/or regiospecific fashions. The reaction of 54 with 6,6-diphenylfulvene gave a mixture of regiosomeric exo-[4+2] and endo-[4+2] adducts. With tropone and 8,8-dicyanoheptafulvene the reaction proceeds via a [4+2] cycloaddition to the C4-C5 and C1-C2 bond of the addend to afford the exo-adduct and desulfurized compound respectively.
IV SPECTROSCOPY

The first UV, NMR and mass spectra were reported for 2- and 3-methyl and 2- and 3-phenyl thiazolo[3,2-a]benzimidazoles. Mass spectral fragmentation patterns were analyzed and the structure of 2- or 3-substituted thiazolo[3,2-a]benzimidazoles was confirmed. UV, IR, NMR and mass spectra of other thiazolo[3,2-a]benzimidazoles were successively reported; the spectroscopic data were correlated with the structures of the examined compounds. Pmr spectra and electron structure of neutral bases and cations of thiazolo[3,2-a]benzimidazole and its methyl derivatives were also investigated. A detailed study dealt with the dependence of chemical shifts from the concentration of the acid. A satisfactory linear correlation was noted between chemical shifts and π-electron density.

The crystal structures of 2,8-dibromo-6,7-dimethyl-3-phenyl thiazolo[3,2-a]benzimidazole (92) and 9-phenacyl- and 9-(p-methylphenacyl)-3-phenyl thiazolo[3,2-a]benzimidazole bromides (93) were determined by X-ray methods. All the compounds are monoclinic and crystallize in space group P2₁/c; the thiazolobenzimidazole system is planar.

UV and mass spectra of 2,3-dihydrothiazolo[3,2-a]benzimidazoles have been reported. Mass spectra fragmentation patterns took place via the open-chain form; some unimolecular decompositions were proposed and analyzed. UV, IR and NMR spectra of 2,3-dihydro-3-hydroxy-3-(p-chlorophenyl)thiazolo[3,2-a]benzimidazol-2-acetic acid (94) and its ethyl ester showed that, in the solid state, these compounds exist in the tricyclic form; in solution at neutral or high pH values the open form (95) is present while closed tricyclic structure (94) is the one assumed in acid medium.
With regard to the synthesis of thiazolo[3,2-a]benzimidazol-3(2H)-ones, the regiochemistry of the obtained products, wherever two isomeric derivatives are likely to be obtained, was established through detailed nmr analysis. The structures of two possible isomers of 6- or 7-substituted thiazolo[3,2-a]benzimidazol-3(2H)-ones (96) and (97) have also been deduced on the basis of Eudpm3-induced nmr spectra of reaction mixture.

\[ R = H, Br, Cl, Me, NO_2, OMe \]

\[ \text{'H- and } ^1\text{C-nmr data of 2-methoxycarbonylmethylenethiazolo[3,2-a]benzimidazol-3(2H)-one have been reported and discussed.} \]

\[ \text{Nmr data of 1H,3H-thiazolo[3,4-a]benzimidazoles (98) 1- and/or 3-substituted have been reported. The detection, by GC/MS of some intermediates, supported the proposed reaction pathway.} \]

\[ R = H, Me; R^1 = H, Me, Et \]
\[ R^2 = \text{alkyl, phenyl} \]

V. BIOLOGICAL ACTIVITY

Bactericidal and fungicidal activity for several derivatives 99, 100, 101 and 102 has been reported.
Compounds 99 exhibit also anthelmintic 45, antinflammatory 176, virucide 42, 177, antipyretic 42, hypotensive 50, anorectic 50, antiulcer 49 and antiviral 177 activity; some of them are also anaphylaxix inhibitors 42. Derivatives 100 are useful as herbicides 10 and their quaternary salts show hypoglicemic activity 30, 31. Some derivatives 100 are able to inhibit alkaline phosphatase of Sarcoma 180/7G 178.

Several compounds 101 were tested as plant growth regulators 111, antitrombotics 112, hypolipemics 112 and anticonvulsants 83, 130. Anthelmintic 48, insecticidal 51, pesticidal 51, anticonvulsant 79, 86, 96, 138, hypotensive 96 activity for compounds 102 have been observed. In addition, they are able to inhibit MAO and succinate dehydrogenase 138.

Numerous studies have been reported for 2,3-dihydro-3-hydroxy-3-(p-chlorophenyl)-thiazolo[3,2-a]benzimidazol-2-acetic acid (WY 13876) (103) which shows antitumor and antimetastatic activity 179, 180. Furthermore, it exhibits immunomodulating effects 181-183 but causes enlargement of the thyroid of rats and dogs 184.

Another compound largely tested is 3-(p-chlorophenyl)thiazolo[3,2-a]benzimidazol-2-acetic acid (WY 18251) (104), obtained by dehydration of WY 13876. This compound shows antineoplastic 30, 185, antimetastatic 186, 187, immunomodulatory 188-190 and antinflammatory 190-191 activity. WY 18251, mixed with influenza vaccine and injected i.m. in mice, potentiated the immune response to the vaccine 31. It is also an inhibitor of mammalian collagenase 192 and is active on the generation of murine T cells suppressor 193. Contrarily to WY 13876, it is not thyrotoxic 184. Biological fate of WY 18251 was also investigated 194-195.

With regard to thiazolo[3,4-a]benzimidazoles, 1H,3H-1-oxo- and 1-imino derivatives (105) showed anthelmintic 118, rodenticide 115, parasiticide 115-117 and antinflammatory 115-117 properties.
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