POTENTIAL BROAD SPECTRUM ANTHelmintics (III)
Design and Synthesis of Certain Arylimidazo[2,1-b]thiazolium Salts

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In a continuation of the programmed scheme for the design and biological testing of certain bridge head fused imidazothiazoles, fourteen new derivatives of 3-aryl-5,6-dihydroimidazo[2,1-b]thiazole are prepared. The Topliss scheme has been followed for the choice of the substituent groups. The structures of the final compounds were confirmed by microanalysis, IR, NMR, and mass spectra.

A wide range of pharmacological activities has been reported for derivatives of imidazothiazole system. They are active against psoriasis(1), they possess anthelmintic(2), vermicidal(3), anti-inflammatory(4), hypoglycemic(5), fungicidal(6), antidepressant(7), antiviral(8), diuretic(9), antituberculous(10), parasiticidal(11), and hypotensive activity(12). Certain derivatives are effective in the treatment of leukemia(13). Development of the broad spectrum anthelmintic tetramisole(14-19) inspired the synthesis of the new compounds of the present investigation in order to study the effect of different possible variations of $\sigma$, $\pi$ and $E_g$ on the biological activity of the parent compounds.

In this work a variety of reduced imidazothiazoles, namely, 3-aryl-5,6-dihydroimidazo[2,1-b]thiazole (I) has been prepared as well as their quaternary salts (II). Too, 3-hydroxy-5,6-dihydroimidazo[2,1-b]thiazole derivatives (III) were prepared in order to investigate the effect of locating a hydroxyl group at position

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- I -
three as well as the variation of the phenyl group at the same position of this ring system on the biological activity.

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} \\
\text{(III)} & \quad \text{(III)}
\end{align*}
\]

The type of substituents was selected according to the Topliss scheme (19). The substituents chosen are capable of discriminating between the hydrophobic, electronic, and steric effects (20), in order to correlate these constants viz., \(\pi\), \(\sigma^*\) and \(K_s\) with anticipated biological activity, if any. In a previous report (21), the substituent groups chosen were p-chloro with \(\pi\) value of +0.70, and \(\sigma^*\) value of +0.23 and the p-bromo which has \(\pi\) value of +1.19, and \(\sigma^*\) value of +0.23. In this report the p-methoxy (\(\pi = -0.40\), and \(\sigma^* = +0.27\)), and p-methyl (\(\pi = +0.60\), and \(\sigma^* = -0.17\)) were selected (22). This is because it is now well established that in many pharmacologically active classes of drugs the activity is +\(\pi^*\)+\(\sigma^*\) dependent (22-27). The choice of p-chloro and p-bromo derivatives of the previous report (21) is a good rationale. If the p-chloro derivative proved to be more potent than the nonsubstituted derivative, it is logic to compare between the hydrophobic character while the \(\sigma^*\) electronic parameter is held constant. Accordingly, the p-bromo derivative with a high \(\pi\) value would present a reasonable approach. If, on the other hand, both the p-chloro and p-bromo derivatives were equally active or less effective than the nonsubstituted, then the choice of the p-methoxy and p-methyl is a good alternative. The former having a high electronic density and a low hydrophobic character, while the latter possessing a low electronic value and a high lipophilic parameter.

It has been reported (28-29), that ionized and unionized species of a compound usually have different distribution characteristics.
which accordingly control its activity. In order to lower the toxicity of the designed compounds as well as to increase their activity, quaternary salts of the aforementioned compounds were formed. Completely ionised quaternary ammonium salts show some biological properties qualitatively akin to those of related amines. In intact animals the completely ionised quaternaries have considerably more difficulty in penetrating the cell membranes and thus have quantitatively quite different distribution patterns (30–32). Oral absorption, access to the central nervous system and intracellular distribution are generally more limited for quaternaries, a fact in favour of increasing the margin of safety to the host on administration of these compounds. With these facts in mind, it was decided to prepare the following quaternary salts:

\[
X = \text{OCH}_3, \text{CH}_3 \]
\[
\text{RY} = \text{CH}_3\text{I}, \text{CH}_2\text{CH}_2\text{I}, \quad \text{iso-C}_3\text{H}_7\text{I}, \quad \text{iso-C}_3\text{H}_7\text{Br}, \quad \text{iso-C}_4\text{H}_9\text{Br}, \quad \text{n-C}_5\text{H}_{11}\text{Br}, \quad p-\text{ClC}_6\text{H}_4\text{COCH}_2\text{Br}, \quad p-\text{BrC}_6\text{H}_4\text{COCH}_2\text{Br}, \quad \text{and} \quad p-\text{CH}_3\text{C}_6\text{H}_4\text{COCH}_2\text{Br}
\]

The choice of these derivatives will enable studying the effect of:

a) Chain length; \(-\text{CH}_3, -\text{C}_2\text{H}_5, \) and \(-\text{C}_5\text{H}_{11}\)
b) Steric factors; \(\text{iso-C}_3\text{H}_7, \) and \(\text{iso-C}_4\text{H}_9\)
c) Electronic availability; \(p\)-chloro and \(p\)-bromo derivatives of the previous report being electron withdrawing by induction versus \(p\)-methyl and \(p\)-methoxy derivatives of this report being electron donating.

The title compounds were prepared through the condensation of the appropriately substituted phenacyl bromide with imidazolidine-2-thione in alcohol and reflux for two hours. The reaction mixture was concentrated under diminished pressure. On cooling, the
hydrobromide salts were separated, then crystallized from ethanol. The bases were liberated by dissolving the hydrobromide salts in distilled water, and rendering alkaline with concentrated solution of ammonia, where the free bases were liberated, filtered and recrystallized from the appropriate solvents.

For preparation of the compounds containing the tautomeric OH group at position three of imidazo[2,1-b]thiazole system, the following reaction was conducted:

A report was published by G.J. Sharpe and R.S. Shadolt\(^7\) for the separation of 2-phenacylthiocimidazolinium salts through the interaction of 2-mercaptoimidazoline in acetone with \(\alpha\)-haloalkylaryl ketones. However, in this work the mass spectra was not presented. With the exception of one derivative, the melting points assigned in that report to the phenacylthiocimidazoles were the same as those assigned in this work for the imidazo[2,1-b]thiazole system. Said reference gave ir data ranging from 1665-1685 cm\(^{-1}\) and this indicates absorption of C = N or C = O \(^{33,34}\). If the ir data reported were due to the C = O group, the melting points should have
been different which is not the case. This is in support with the conclusion that these values are due to C = N, indicating that the reaction proceeded in one step with direct formation of the fused ring structure of 3-aryl-5,6-dihydroimidazo[2,1-b]thiazole.

In the present investigation, trials have been made to separate the phenacyltioimidazolium salts by carrying out the reaction under mild conditions. This proved unsuccessful and only the closed ring system was obtained. A plausible mechanism for this reaction has been suggested in our earlier publication (21).

Infrared spectra for the hydrobromide salts showed -NH stretching absorption band and also showed C = C conjugated with an aromatic ring as well as C = N stretching vibration bands at 3520 - 3400 cm\(^{-1}\) and 1689 - 1471 cm\(^{-1}\) respectively. The bases showed no C = O or -NH stretching absorption bands; however, they showed C = O at 1625 cm\(^{-1}\) and C = N at 1689 - 1471 cm\(^{-1}\) stretching vibration bands. Spectra for some of the quaternary salts also showed C = C as well as -NH stretching vibration bands at 1700 cm\(^{-1}\) and 3520 - 3400 cm\(^{-1}\) respectively. Spectra for 3-hydroxy derivatives showed a tautomeric -OH group at 3300 - 3520 cm\(^{-1}\) as well as C = O at 1700 cm\(^{-1}\).

In the present work, quaternization was effected through mixing the isopropanol solutions of both imidazothiazoles with the alkyl halides or \(\alpha\)-haloketones. The reaction mixture was heated under reflux on a steam bath, then cooled, and the product which separated out was filtered and recrystallized from the appropriate solvent.

It has been found that primary alkyl halides gave better yields than secondary, and the iodides were more reactive than the bromides; findings complying with what is reported for relative activity of these halides. The reaction with the phenacyl bromides gave always good yields.

**EXPERIMENTAL**

*\(p\)-Substituted acetophenones*: The required substituted acetophenones were prepared according to a reported method (35).
**p-Substituted phenacyl bromides** : These were prepared by bromination of the appropriate acetophenone in glacial acetic acid following a reported procedure (36).

**Imidazolidine-2-thione** : This compound was prepared in 90% yield; m.p. 197 - 198° as reported (37).

**3-Aryl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromides** ; Table (I)

In a 100 ml round bottomed flask connected to a double surface reflux condenser was placed the appropriate phenacyl bromide (0.01 mole) dissolved in absolute ethanol (25 ml). Imidazolidine-2-thione (0.01 mole) was added to this mixture and the flask was heated on a steam bath under reflux for two hours. The mixture was cooled, and the product which separated out was filtered at the pump, washed with absolute alcohol, drained well and then recrystallized from boiling water.

![Chemical Structure]

**Table (I) 3-Aryl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromides.**

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**3-Aryl-5,6-dihydroimidazo[2,1-b]thiazoles** ; Table (II)

These bases were liberated by dissolving the appropriate hydrobromides in distilled water and rendering alkaline with concentrated solution of ammonia. The precipitated bases were filtered at the pump, washed well with water, dried and recrystallized from ethanol.
Table (II) 3-Aryl-5,6-dihydroimidazo[2,1-b]thiazoles.

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3-Aryl-7-substituted-5,6-dihydroimidazo[2,1-b]thiazolium halides: Table (III)

In a 100 ml round bottomed flask fitted to a reflux condenser, the appropriate 3-aryl-5,6-dihydroimidazo 2,1-b thiazole (0.005 mole) was dissolved in 2-propanol (15 ml). To this solution was added a solution of the appropriate alkyl halide or the substituted phenacyl bromide (0.005 mole) in 2-propanol (10 ml). The reaction mixture was heated under reflux on a steam bath for two hours, and then allowed to cool. The product that separated was removed by filtration under suction, dried and recrystallized from the appropriate solvent.

3-Hydroxy-5,6-dihydroimidazo[2,1-b]thiazole:

In a 100 ml round bottomed flask fitted to a reflux condenser, sodium salt of imidazolidine-2-thione (0.01 mole) was dissolved in 2-propanol (15 ml). To this solution was added a solution of chloroacetic acid (0.01 mole) in 2-propanol (15 ml). The reaction mixture
was heated under reflux on a steam bath for two hours, cooled and the product that separated was removed by filtration under suction, dried and recrystallized from isopropanol into white crystalline needles m.p. 181-183°, yield: 67.24%.
Microanalysis: C%: Calcd 34.18 Found 34.10
H%: Calcd 2.27 Found 2.70

3-Hydroxy-2-phenyl-5,6-dihydroimidazo[2,1-b]thiazole:

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{S} & \quad \text{N} \\
\text{Ph} &
\end{align*}
\]

In a 100 ml round bottomed flask connected to a double surface condenser was placed \( \gamma \)-bromophenylacetic acid (0.01 mole) dissolved in absolute ethanol (20 ml). Imidazolidine-2-thione (0.01 mole) in absolute ethanol (20 ml) was added to this mixture and the flask was heated on a steam bath under reflux for two hours. The mixture was cooled and the product which separated out was filtered at the pump, dried and recrystallized from absolute ethanol into needles, m.p. 178-180°, yield: 68.80%.
Microanalysis: N% calcd 12.84, found 13.10
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**CALC'D. FORMULA**

**MOL. FORMULA**

**MOL. WEIGHT**

**X**

**m.p.**

**X**

**NO.**

**TABLE (III)**

3-COMPONENTS [7-1-8] 5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'-5'-1-4'-1-8'
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Table (III) continued
REFERENCES


10) H.L.Bell, U.S. 3n 853n 872(1974); through Chem. Abstr. 82, 140202 k(1975).


II
18) Ibid., 1226 (1966).
تصميم وتخليق مركبات حلوقية غير شجاعة من اسلاح
- تأسيس - تحالف هيدروآيزو (آيزو) النمازسي الجزء الثالث
لهند عبد الناصر القوي - محمد طافع عبد القادر - عبد الحميد نجيب أحمد

تم في هذا الجزء من البرنامج تصميم وتخليق أربعة مركبات جديدة من
مختلطات النيتروسازول ذات الرأس البروتيني. ويفضل أن تتضمن
تستويز- أر- هيدروآيزو (آيزو - ب) النمازس - تستيؤز - أر-
أجل استكمال تأهيلها داخل مجموعة التحكيم في الوصف.
والعمل تغيير وضع مجموعة الفينيل في الكيان رقم - 2 - لهذا النظام
الجميل في تأسيس البيولوجيا.

ولقد احتوى الانواع المبكرة وقبلها لجداول تحليلات، وذلك كأن البديعات
الخاصة لها وقدرة على التماس- بين الهيدروآيزو والتأثيرات الإلكترونية والتأثيرات
المورفولوجية في أجل البيولوجيا بين تلك التحاليل، و عليه، مع الفائدة
البيولوجية لبعض هذه المركبات أن وجدنها.

لقد تم بالإضافة إلى تغيير هذه المركبات بعد التحليل الدقيق لمكوناتها واستخدام الأهمية لسوخ الخصائص وكذلك
طبيعة الأسماء النموذجية للعديد من العناصر.