Bull. Pharm. Sci. Assiut Univ.

Vol. I, PP. I-I3 (I978)

POTENTIAL BROAD SPECTRUM ANTHELMINTICS (III)
Design and Synthesis of Certain Arylimidazo[2.1-b]thiazolium Salts*

M.A.Eldawy, Dept. of Pharm. Chem., Faculty of Pharmacy, Univ. of Tanta; M.A.Abdel Kader, and A.N.Ahmed, Dept. of Pharm. Chem. Faculty of Pharmacy, Univ. of Assiut, Assiut/EGYPT

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.

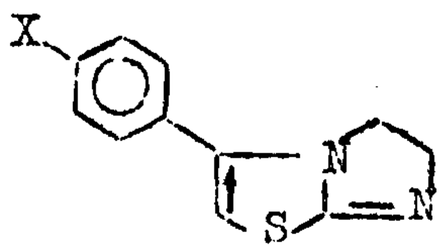
A wide range of pharmacological activities has been reported for derivatives of imidazothiazole system. They are active against psoriasis[1], they possess anthelmintic[2], vermicidal[3], anti-inflammatory[4], hypoglycemic[5], fungicidal[6], antidepressant[7], antiviral[8], diuretic[9], antituberculous[10], 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 σ, π and E_s 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-dihydro-imidazo[2.1-b]thiazole derivatives (III) were prepared in order to investigate the effect of locating a hydroxyl group at position

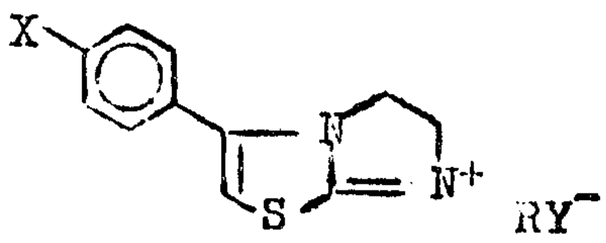
---

* Abstracted from the dissertation presented by A.N.Ahmed, in partial fulfilment of the M.Sci. (Pharm.Chem.) requirement, Univ. of Assiut, 1976. Presented before the Congress of Arab Pharmacists Union, Kuwait, 8-11 Nov. 1976.

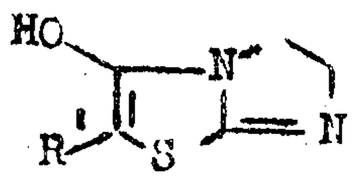
three as well as the variation of the phenyl group at the same position of this ring system on the biological activity.



(I)



(II)



(III)

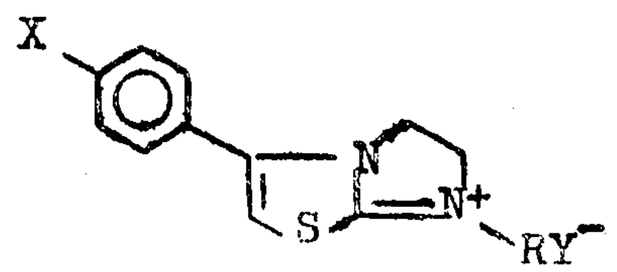
The type of substituents was selected according to the Topliss scheme[19]. The substituents chosen are capable of discriminating between the hydrophobic, electronic, and steric effects[20], in order to correlate these constants viz. π , σ and E_s with anticipated biological activity, if any. In a previous report[21], the substituent groups chosen were p-chloro with π value of +0.70, and σ value of +0.23 and the p-bromo which has π value of +1.19, and σ value of +0.23. In this report the p-methoxy (π = -0.40, and σ = +0.27), and p-methyl (π = +0.60, and σ = -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 σ electronic parameter is held constant. Accordingly, the p-bromo derivative with a high π 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 then 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 ionised and unionised 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 :

$X = OCH_3$, CH_3

RY= CH_3I , CH_3CH_2I ,
iso- C_3H_7I , iso- C_3H_7Br
iso- C_4H_9Br, n- $C_5H_{11}Br$
p-$ClC_6H_4COCH_2Br$,
p-$BrC_6H_4COCH_2Br$, and
p-$CH_3C_6H_4COCH_2Br$

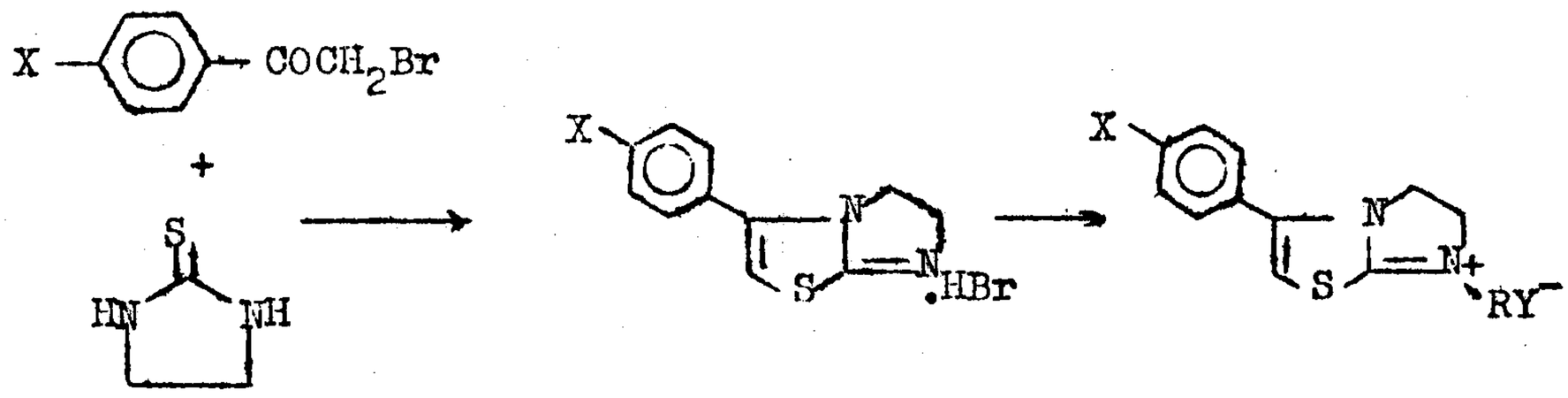


The choice of these derivatives will enable studying the effect of :

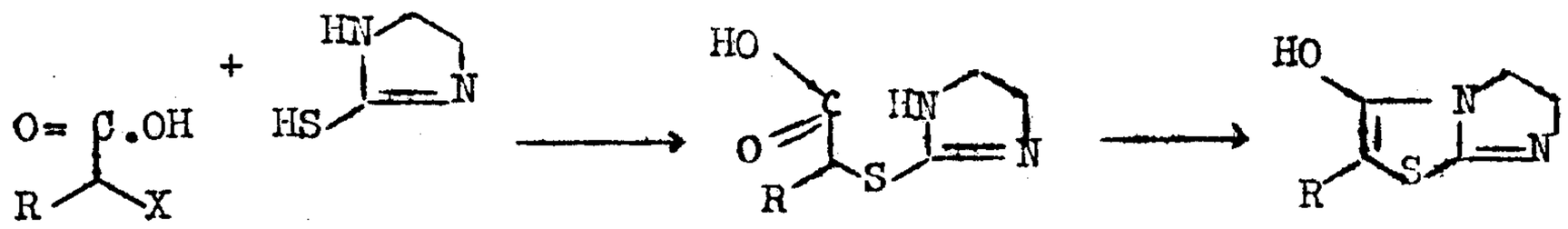
a) Chain length ; $-CH_3$, $-C_2H_5$; and $-C_5H_{11}$
b) Steric factors ; iso-C_3H_7 , and iso-C_4H_9
c) Electronic availability ; p-chloro and p-bromo derivatives of the previous report being electron withdrawing by induction versus p-methyl and p-methoxy derivatives of this report being electron donating.

The title compounds were prepared through the condensation of the appropriately substituted phenacylbromide 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-phenacylthioimidazolinium salts through the interaction of 2-mercaptoimidazoline in acetone with ∝-haloalkyl-aryl 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 phenacylthioimidazoles 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 phenacylthioimidazolium 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 = C 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 α-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.

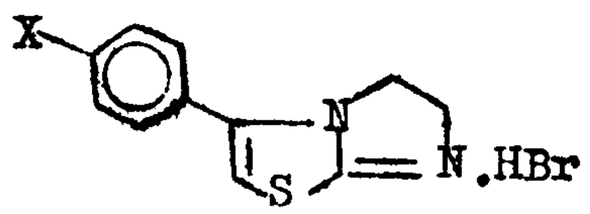
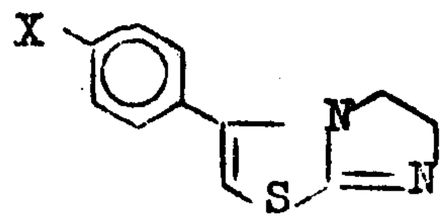


Table (I) 3-Aryl-5,6-dihydroimidazo-[2.1-b]thiazole hydrobromides.

No	X	m.p. °C	Yield %	Mol.Formula		Microanalysis Calcd	Found
1	$-CH_3$	250-252	75.9	$C_{12}H_{13}BrN_2S$	N S Br	9.42 10.77 26.93	9.20 11.20 27.00
2	$-OCH_3$	228-230	64.5	$C_{12}H_{13}BrN_2OS$	N	11.94	11.80

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 recrystallised from ethanol.



3-Aryl-5,6-dihydro-

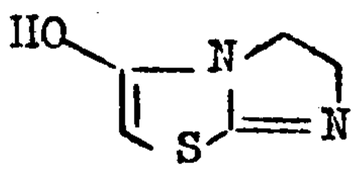
Table (II) imidazo[2.1-b]thiazoles.

No	X	m.p. °C	Yield %	Mol.Formula		Microanalysis Calcd	Found
3	$-CH_3$	150-152	76.19	$C_{12}H_{12}N_2S$	N S	12.96 14.81	12.60 14.31
4	$-OCH_3$	179-181	95.65	$C_{12}H_{12}N_2OS$	S	13.79	13.70

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 filteration under suction, dried and recrystallized from the appropriate solvent.

3-Hydroxy-5,6-dihydroimidazo[2.1-b]thiazole :

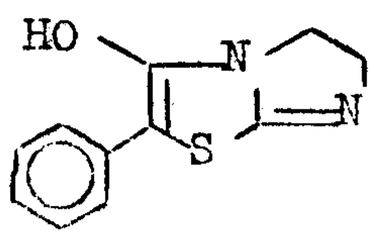


In a 100 ml round bottomed flask fitted to a reflux condenser, sodium salt of imidazolidine-2-thione (0.01 mole) was dissolved in 2-propanol (15 ml). To this solution was added a solution of chloro-acetic acid (0.01 mole) in 2-propanol (15 ml). The reaction mixture

was heated under reflux on a steam bath for two hours, cooled and the product that separated was removed by filteration under suction, dried and recrystallized from isopropanol into white crysalline needles m.p. 181-183°, yield: 67.24%.

Microanalysis : C% : Calcd 34.18 Found 34.10
H% : Calcd 2.27 Found 2.70

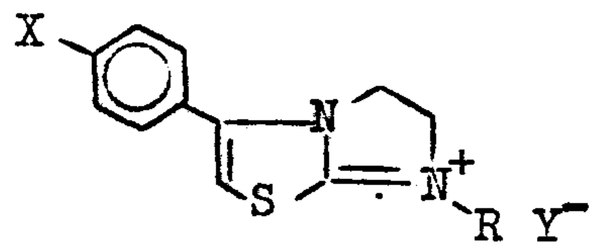
3-Hydroxy-2-phenyl-5,6-dihydroimidazo[2.1-b]thiazole :



In a 100 ml round bottomed flask connected to a double surface condenser was placed α-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

Table (III) : 3-Aryl-7-substituted-5,6-dihydro-imidazo[2.1-b]thiazolium halides



No.	X	R	Y	m.p. °C	Yield %	Mol. Formula		Microanalysis Calcd.	Found
1	$-CH_3$	$-CH_3$	I	125-7	85.7	$C_{13}H_{15}IN_2S$ [a]	C H N	43.37 4.18 7.82	42.70 4.20 7.80
2	$-CH_3$	$-CH_2CH_3$	I	151-3	67.5	$C_{14}H_{17}IN_2S$ [b]	N	7.52	7.70
3	$-CH_3$	$-CH_2CH(CH_3)_2$	Br	268-70	50.2	$C_{16}H_{21}BrN_2S$ [b]	N	7.93	7.90
4	$-CH_3$	$-CH_2COC_6H_4Cl(p)$	Br	253-5	61.9	$C_{20}H_{18}BrClN_2OS$ [a]	C H	49.50 4.00	49.00 3.80
5	$-CH_3$	$-CH_2COC_6H_4Br(p)$	Br	198-200	58.9	$C_{20}H_{18}Br_2N_2OS$ [a]	N	5.66	6.20
6	$-OCH_3$	$-CH_3$	I	186-8	81.1	$C_{13}H_{15}IN_2OS$ [b]	C H N	41.71 4.01 7.48	41.30 4.50 7.20
7	$-OCH_3$	$-CH_2CH_3$	I	143-5	56.7	$C_{14}H_{17}IN_2OS$	C H N	43.29 4.38 7.21	42.90 4.00 7.00
8	$-OCH_3$	$-CH(CH_3)_2$	Br	254-6	31.4	$C_{15}H_{19}BrN_2OS$ [b]	C H N	50.07 5.50 7.88	49.90 4.70 8.30

Table (III) Continued

No	X	R	Y	m.p. °C	Yield %	Mol.Formula		Microanalysis Calcd.	Found
9	$-OCH_3$	$-CH_2CH(CH_3)_2$	Br	258-60	48.2	$C_{16}H_{21}BrN_2OS$ [b]	N	7.50	8.00
10	$-OCH_3$	$-(CH_2)_4-CH_3$	Br	152-4	28.7	$C_{17}H_{23}BrN_2OS$ [b]	C H	53.26 6.00	53.00 6.50
11	$-OCH_3$	$-CH_2COC_6H_4Cl(p)$	Br	248-50	63.1	$C_{20}H_{18}BrClN_2O_2S$ [b]	N	5.01	6.30
12	$-OCH_3$	$-CH_2COC_6H_4Br(p)$	Br	243-5	50.9	$C_{20}H_{18}Br_2N_2O_2S$ [b]	C H N	47.05 3.52 5.49	46.90 3.80 5.00
13	$-OCH_3$	$-CH_2COC_6H_4CH_3(p)$	Br	227-9	63.6	$C_{21}H_{21}BrN_2O_2S$ [b]	C H	46.62 4.71	46.60 4.40

a) Ethyl alcohol

b) Isopropanol

REFERENCES

1) Voorhees John; J. Ger. Offen. 2,401,446(1974). U.S. Appl.,342, 012(1973); through Chem. Abstr. 82,35028 K(1975).

2) John Edson, Halmos, Imre A.(American Cyanamid Co.), Ger. Offen. 2,429,227(1975); through Chem. Abstr. 82,170932 r(1975).

3) Spicer D. Larry, Hand John J.; U.S. 3,792,166(1974); through Chem. Abstr. 81,3919 q(1974).

4) Michio Otsuka, Katsuyuki Obta, Kano Sacbaki; Japan Kakai, 4470, 986(1974); through Chem. Abstr. 81,136142 c(1974).

5) Kuhla-Donald E.,(Pfizer Inc.) U.S. 3,860,718(1975); through Chem. Abstr. 82,140133 p(1975).

6) Haugwitz D. Rndigr, Narayahan, L.Venkatachola (Squibb, E.R. and Sons Inc.) U.S. 3,864,353(1975); through Chem. Abstr. 82, 156323 m(1975).

7) G.J.Sharpe, R.S.Shadbolt, A.Ashford, J.W.Ross, J.Med.Chem.,14, (10),977-82(1971) (Eng).

8) Societe des Usines Chimiques, Rhone poulenc Fr.M.7391(1969); through Chem. Abstr. 78,43477 p(1973).

9) Houlihan, J.William, E.Manning Robert, U.S. 3,671,534(1972); through Chem. Abstr. 77,88506 t(1972).

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

11) Hashimato, Youshinobu, Kano, Saburo, Arima, Yoshikatsu; Japan Kakai 73,68,719(1973); through Chem. Abstr. 80,34391 v(1974).

12) E.Manning Robert, U.S. 3,555,039(1971); through Chem. Abstr 74,10057 v(1971).

13) M.A.Chirigos, Fuhrman F.Pryor, J. Cancer Res. 35(4),927-31 (1975) (Eng.); through Chem. Abstr. 83,37631 w(1975).

14) D.C.I.Thienpont et al, Nature 209,1084(1966).

15) A.H.M.Raeymaekers, F.T.N.Allewijin, P.A.J.Janssen, J.Med.Chem., 2,545(1966).

16) A.H.M.Raeymaekers, L.F.C.Roevens, and P.A.J.Janssen, Tetrahedron Letters, 16,1467(1967).

17) L.A.Cort, J.Chem.Soc., 3456(1965).

18) Ibid., 1226(1966).

19) J.Topliss, J.Med.Chem., 15, 1005(1972).

20) J.Hine,"Physical Organic Chemistry" 2 nd ed.,Mac Graw, New York p. 87(1962).

21) M.A.Eldawy, M.A.Abdel Kader, A.N.Ahmed, Proc. XIV th Conf. of Pharmaceutical Sci. Cairo, Dec. 7-10,Egypt(1975),page 112.

22) T.Fujita, J.Iwasa, and C.Hansch, J.Amer.Chem.Soc.,86,5175(1964)

23) H.H.Jaffe, Chem.Rev., 53,19(1953).

24) J.Iwasa, T.Fujita, and G.Hansch, J.Med.Chem., 8,150(1965).

25) E.Miller, and C.Hansch, J.Pharm. Sci.,56,92(1967).

26) A.Seo, C.Hansch, and D.Elkeus, Chem.Rev., 71,551(1971).

27) Y.Martin, and W.J.Dunn, J.Med.Chem., 16,578(1973).

28) E.J.Ariens,"Molecular Pharmacology",vol. I, Academic Press, New York(1964).

29) H.Davason, and J.F.Danielli; The permeability of natural membranes; through Alfred Burger "Medicinal Chemistry" 3 rd ed., Wiley-Interscience,p. 137(1970).

30) A.Albert,"Selective Toxicity", 4 th ed.,Wiley,New York (1968).

31) E.W.Gill, Progr.Med.Chem.,4,39(1965).

32) B.R.Baker,"Design of Active Site Directed Irreversible Enzyme Inhibitors", Wiley, New York (1967).

33) M.Feter, and L.C.King, J.Org.Chem.,26,828(1961).

34) R.L.Silverstein, G.C.Bassler,"Spectrometric Identification of Organic Compounds",Wiley-International ed.,p.64.

35) Noller and Adams; J.Amer.Chem.Soc.,46,1839(1924).

36) W.D.Langley; Org.Synthesis Collective, 1,127(1941).

37) C.F.H.Allen, C.O.Edens and J.Ames Van Allen; Org. S nthesis, Collective,III, p.394.

تصميم وتخليق مركبات حلقية غير متجانسة من امـلاح

٣ـ أريـل ـ٥ر٦ـ ثنائى هيدرو اميدازو (٢ر١ـب) الثيازول الجزء الثالث

محمـد عبد الفتـاح الفـوى ـ محمود عاطف عبدالقادر ـ عبد الحميـد نجيب احمد

تـم فى هـذا الجـزء من البرنامج تصميم وتخليق اربعـة عشـر مركبا جـديدا مـن مشـتقات الاميـدازوثيـازول ذات الرأس النيستروجينى . وايضـا تـم تخليـق مشتقـات ٣ـ هيـدروكسـى ـ٥ر٦ ـ ثنـائى هيـدرو اميـدازو (٢ر١ ـ ب) ثيـازول مـن أجـل استكشـاف تأثيـر ادخـال مجمـوعة الهيدروكسى فى الموضـع ـ ٣ ـ وبالمثـل تغييـر وضـع مجمـوعة الفينيـل فى المكـان رقـم ـ٢ـ لهـذا النظـام الحـلقى عـلى التأثيـر البيولوجـى .

ولقـد اختيرت الانـواع البـديلة طبقـا لجدول تولـس ، ولقـد كانت البديـلات المختـارة لهـا القـدرة عـلى التمييـز بيـن الهيدروفوبك والتأثيـر الالكترونى والتأثيـر الفـراغى مـن أجـل الربـط بين تلك الثوابت π و σ و E_s مـع الفاعليـة البيولوجيـة لهـذه المركبـات ان وجـدت.

ولقـد تـم بالاضـافة الى تعييـد هـذه المركبـات اثبـات صورتهـا النهائيـة عـن طـريق التحليـل الدقيـق لعناصـرها وباستخدام الاشعـة فـوق الحمـراء وكـذلك طـريق الرنيـن النـووى المغناطيسـى وطيـف الكتـلة.