Synthesis of a Series of Novel Heterocyclic Compounds from Halogenated 3,5-dimethyl-1,1-dioxo-1,2-thiazines

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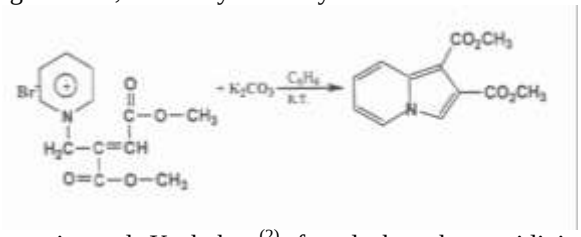
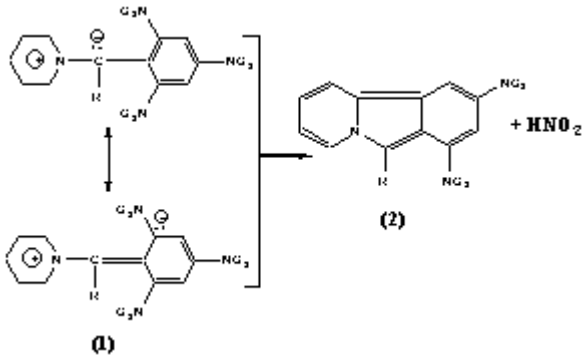
Abstract:
Two novel classes of heterocyclic compounds containing nitrogen atom at a bridgehead position have been synthesized by a convenient two-step procedure. In addition to biological studies, the structure of the new products were confirmed using elemental analysis, u.v-, i.r-, ^{1}H- and ^{13}C-n.m.r spectroscopy.

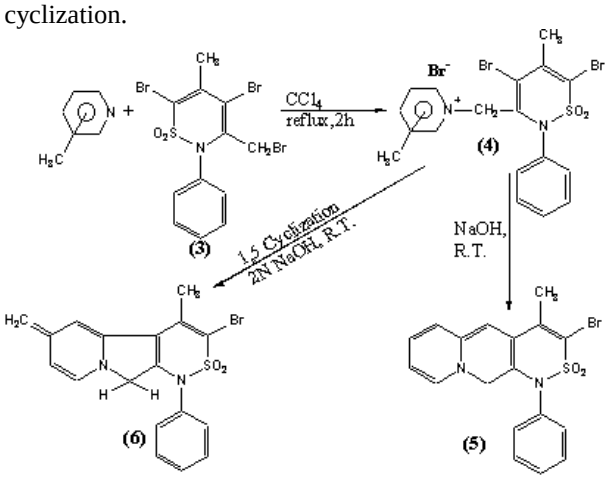
Introduction:
The positively charged hetero-atom in a pyridinium salt has an activating influence on a methylene group attached to it. If this methylene group is also activated by another electron-attracting or electron-accepting group, the pyridinium salts with an appropriate base undergo intramolecular 1,5-dipolar cyclization to form systems having a nitrogen atom at a bridgehead position. For example, the 1-(2,3-bis methoxy carbonyl allyl) pyridinium bromide undergo base catalyzed ring closure to give the 1,2-dimethyl carboxylate indolizine [(1)].



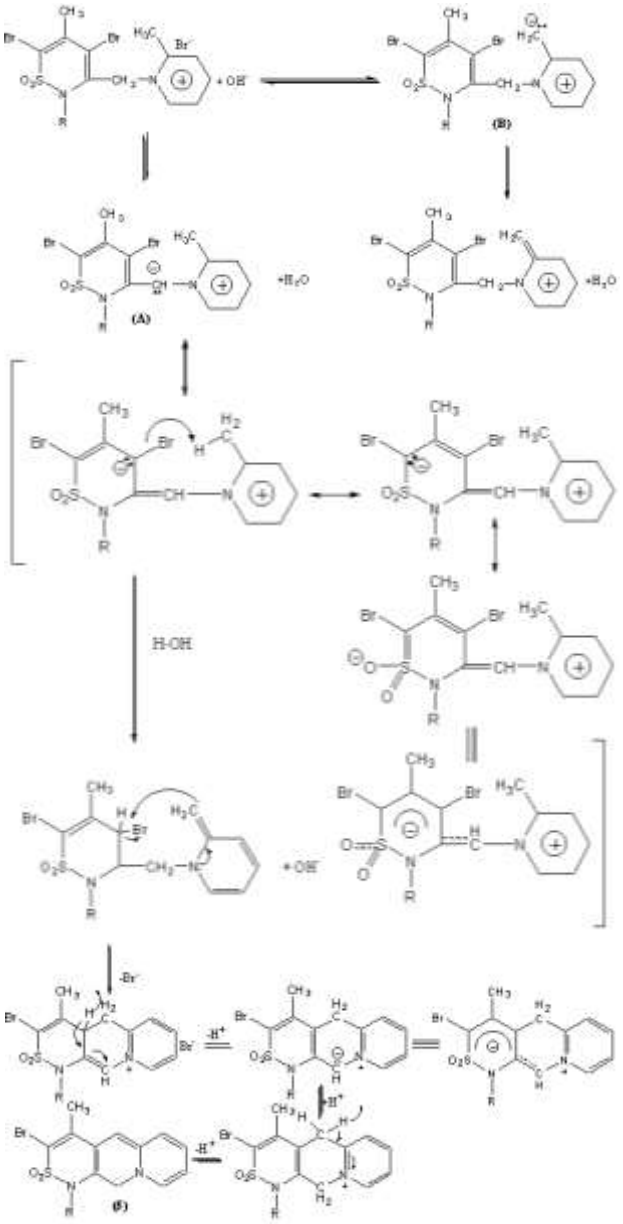
Augstein and Krohnke [(2)] found that the pyridinium picryl betaines of type (1) will undergo intramolecular 1,5-cyclization and subsequent loss of nitrous acid to give the indolizine derivatives (2) in very high yield.



In this paper a series of methyl pyridinium bromide salts prepared as intermediate compound (4) by the reaction of methyl pyridines and halogenated 1,2-thiazines (3)[(4,5)] and during this work it was found that 4-methyl pyridinium bromide salt undergo 1,5-cyclization while 2-methyl pyridinium bromide salts follows another type of cyclization.

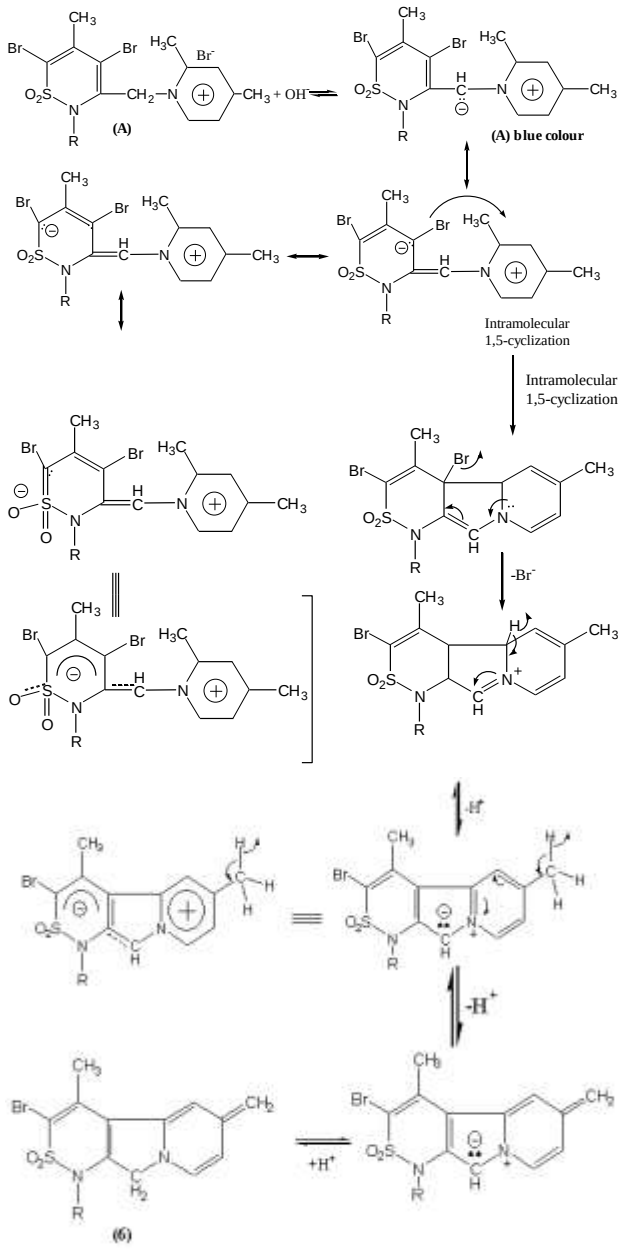


Result and Discussion:
When an aqueous solution of 2-methyl pyridinium bromide salt (4) treated with sodium hydroxide (2N) solution at room temperature, a blue colour has been appeared and then faded, the addition of alkali solution is continued until the colour no longer is developed. This blue colour, which is attributed to a reactive intermediate compound, is remained about one minute then changed to red-brown and precipitated as a final product. In this reaction as we believe, the hydroxide ion (-OH) as nuclophile, does not attack the pyridinium ring since in infrared spectra of the products, peaks due to OH and NH bomd streaching in the region of 3200-3500 cm^{-1} was not observed. Now, we attribute the appearance of blue colour to the transienl presence of pyridinium methylide in the form of (A) and not (B), because the N-methylene protons due to influence of the neighboring electron withdrawing group pyridinium ring in one band and thiazinyl ring in another hand, is more acidic than the 2-methyl protons at α-positions of pyridinium ring. Then the pyridinium methylide as in the case of pyridinium picryl methylide [(2)], dose not undergo intermolecular 1,5-cyclization, presumably because one of the two α-positions in pyridinium ring occupied by methyl group and its rendering steric hindrance around reaction center, then, the pyridinium methylide simultaneously passed a number of steps, as shown in the suggested mechanism as follows, to give compound (5)[(4)].



Scheme (1): Suggested mechanistic pathway of the reaction of 2-methylpyridinium bromide with hydroxide ion.

As in the case of the previously mention 2-methylpyridinium bromide, the reaction of 4-methylpyridinium bromide with sodium hydroxide solution and at room temperature. gives 4-methylpyridinium methylides (A), as shown in the suggested mechanism below, which has a blue colour and this colouration could be attributed to the delocalization of its negative charge in 1,2-thiazinyl ring, which is similar to pyridinium picryl methylide [(2)], undergoes intramolecular 1,5-cyclization to give compound (6). The biological activities of these prepared compounds (5,6) were tested against *Escherichia Coli* and *Staphylococcus Aureus*, it was found that they are biologically inactive.



Scheme (2): Suggested mechanistic pathway of the reaction of 4-methylpyridinium bromide with hydroxide ion**.**

Experimental:

Melting points were determined on a Toshinwal-Electrothermal melting point apparatus. IR-spectra were recorded as KBr disc on a Thermo Mattson IR-300 spectroscopy; the abbreviation s = strong, m = medium, w = weak are used throughout. The ^{1}H-NMR spectra were taken using Bruker AM-400 (400 MHz) in $CDCl_3$; the abbreviation s = singlet, d = doublet, t = triplet, m = multiplet are used throughout. The ^{13}C-NMR spectra were recorded using Bruker AM-400 (400 MHz) in $CDCl_3$. elemental analysis was carried out on a 1106 Carlo Erba elemented analyzer.

UV absorption spectra were measured by perkin Elmer Hitachi spectrometer. All the reactions were routinely cheeked by TLC on silica gel using benzene and toluene as a solvent.

4,6-dibromo-3-bromomethyl-5-methyl-2-(substituted phenyl) - 2H - [1,2] thiazine-1,1-dioxide (3):

The title compounds were prepared as described in the literature [3,4,5].

3-bromo-1-(substituted phenyl)-4-methyl-1 H, 9H-2-thia-1, 8a-diaza-anthracene-2, 2-dioxide(4), (5):

Equimolar amounts of 2-methyl pyridine with 4,6-dibromo-3-bromomethyl-5-methyl-2-substituted phenyl-2H-[1,2] thiazine-1,1-dioxide (3) in acetonitrile as a reaction medium was refluxed for two hours in a water bath. When the reaction was completed, the obtained solution was cooled to room temperature then 75 ml of water and 2N sodium hydroxide solution were added until precipitation, respectively. The precipitated product was collected by filteration and washed several times with water then air dried and recrystallized from benzene. The physical properties, spectroscopic and elemental analysis data of the prepared compounds are given in Tables (1, 2,3,4,5 and 6).

Table (1): The percentage yields, m.p. ^oC and R_f of the preparing compounds (5 and 6)

Compounds		R	m.p. ^oC	Yield %	R_f (Benz.-Tolu.)
5	a	H	128-130	41	0.60
	b	4-CH_3	205-206	37	0.65
	c	4-Cl	210-212	42	0.80
	d	4-Br	145-148	30	0.75
	e	2-OCH_3	158-159	39	0.61
6	a	H	120-121	43	--
	b	4-CH_3	164 dec	30	0.47
	c	4-Cl	168-170	50	0.58
	d	4-Br	170 dec	41	0.58
	e	2-OCH_3	143-145	35	0.78

Table (2): Uv-absorptional data of compounds (5 and 6)

Compounds		λ_{max1} nm	λ_{max2} nm	λ_{max3} nm
5	b	253	301	320
	c	253	303	316
	d	251	305	317
6	a	248	302	318
	b	250	305	320
	c	245	297	317
	d	249	301	319
	e	242	285	315

Table (3): Analytical data of compounds (5 and 6)

Compounds		Calculated			Found		
		% C	% H	% N	% C	% H	% N
5	c	49.39	3.22	6.39	49.25	2.91	6.34
	d	44.83	2.92	5.93	44.53	2.78	5.58
	e	52.65	3.95	6.49	52.3	3.92	6.44
6	c	49.39	3.22	6.39	48.87	3.15	6.21
	d	44.83	2.92	5.82	43.80	2.92	5.70

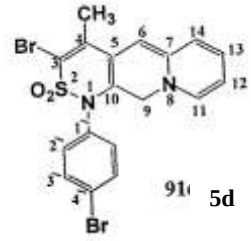
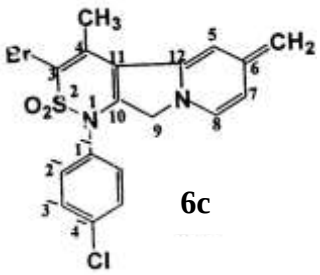
Table (4): The IR spectral data of compounds (5 and 6)

Compounds		(ν' SO_2) cm^{-1} Asym.	(ν' SO_2) cm^{-1} Sym.	(ν' S-N) cm^{-1}	(ν' C-N) cm^{-1}	out of plane deformation of aromatic proton
5	a	1369(s)	1175(s)	920(w)	1265(m)	695(s) 760(s)
	c	1362(s)	1176(s)	929(m)	1251(m)	827(m)
	d	1357(s)	1173(s)	919(w)	1249(m)	821(m)
6	a	1351(s)	1169(s)	918(w)	1264(m)	694(s) 762(s)
	d	1353(s)	1167(s)	915(w)	1269(w)	822(m)
	e	1355(s)	1180(s)	930(m)	1265(s)	763(s)

Table (5): The ^{1}H-NMR data of compounds (5 and 6)

Compounds	δ ppm	Assignment
5d	2.41(s)	4-methyl protons
	3.36(s)	Methylene protons (-CH_2-)
	4.95(s)	Olefinic protons (-CH-) of1, quinalizodiene moiety
	6.98(d) and 7.30(d)	Aromatic protons of p-bromophenyl ring
6c	2.48(s)	4-methyl protons
	3.53(s)	Methylene protons (-CH_2-)
	4.15(s)	Terminal methylene group
	7.22(d) 7.24(d) and 7.27(s)	Olefinic protons (-CH-) of1, pryrrocoline moiety
	7.17(d) and 7.60(d)	Aromatic protons of p-chlorophenyl ring

Table (6): The ^{13}C-NMR spectral data of compounds (5 and 6)

Compounds	Chemical shifts (δ) in ppm							
 **5d**	C_3	117.51	C_6	110.87	C_{11}	135.82	C'_1	132.62
	C_4	138.46	C_7	126.02	C_{12}	118.96	C'_2	130.23
	C_4-CH_3	19.98	C_9	31.21	C_{13}	126.71	C'_3	128.12
	C_5	116.15	C_{10}	122.16	C_{14}	123.87	C'_4	128.83
 **6c**	C_3	116.97	C_6	123.58	C_9	39.72	C'_1	131.86
	C_4	139.12	C_6=CH_2	114.22	C_{10}	112.29	C'_2	133.35
	C_4-CH_3	22.49	C_7	125.95	C_{11}	110.15	C'_3	129.96
	C_5	119.21	C_8	131.24	C_{12}	129.38	C'_4	136.73

3-bromo-1-(substituted phenyl)-4- methyl -6-methylene-6, 9-dihydro-1 H-2-thia-1, 8a-diaza-fluorene-2, 2-dioxide(6):

Preparation of compounds (6) from the reaction of methyl pyridine with 4,6-dibromo-3-bromomethyl-5-methyl-2-substituted phenyl-2H-[1,2] thiazine-1,1-dioxide (3) were followed by the same procedure which described previously. The physical properties, spectroscopic and elemental analysis data of prepared compounds are given in Tables (1,2,3,4,5 and 6).

References:

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تحضير سلسلة جديدة من مركبات 3,5-dimethyl-1, 1-dioxo-1, 2-thiozines المهلجنة

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الملخص:

تم تحضير صنفين حديثين من المركبات غير المتجانسة التي تحتوي على ذرة النتـروجين بطريقـة ملائمـة ذات خطـوتين، بالإضـافة إلـى الدراسـات البيولوجية، تم التأكد من تركيب النواتج الجديدة باستعمال تحليل العناصر، أطيـــــــــاف، u.v ، i.r. ، ^{13}C-nmr ^{1}H-nmr,