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BASE INDUCED REACTIONS OF N-METHYL QUATERNARY SALTS OF THIOPHENE CONDENSED 1-AZA-BICYCLO[3.3.1.]NONANES

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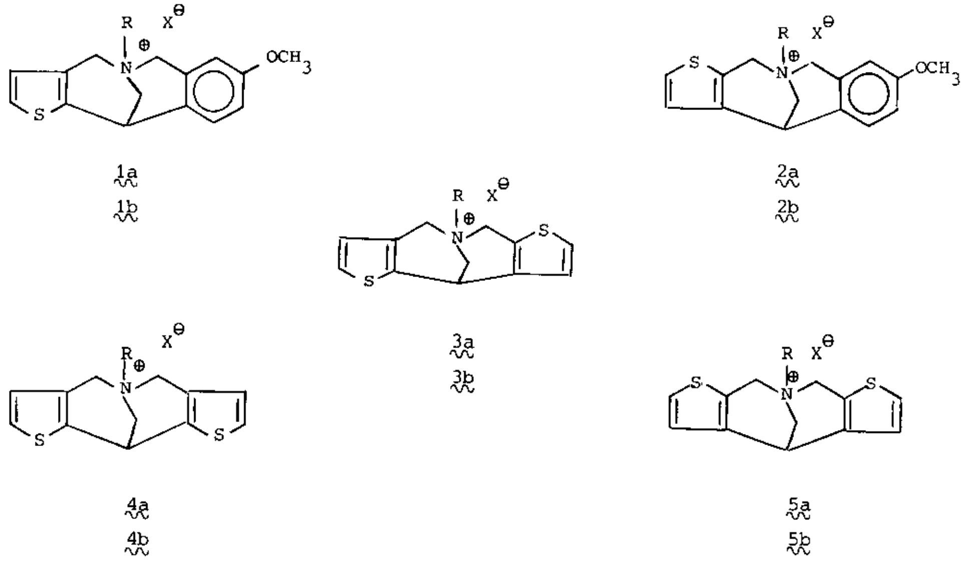
Abstract - Reactions of N-methyl quaternary salts of thiophene condensed 1-aza-bicyclo[3,3,1]nonanes with various bases were examined in order to obtain preferentially Hofman elimination or Stevens rearrangement.

In the preceding paper we reported[1] the synthesis of tetracyclic compounds (1a - 5a) (R=H, X= Cl) (Scheme I)

Scheme I



1a
1b

2a
2b

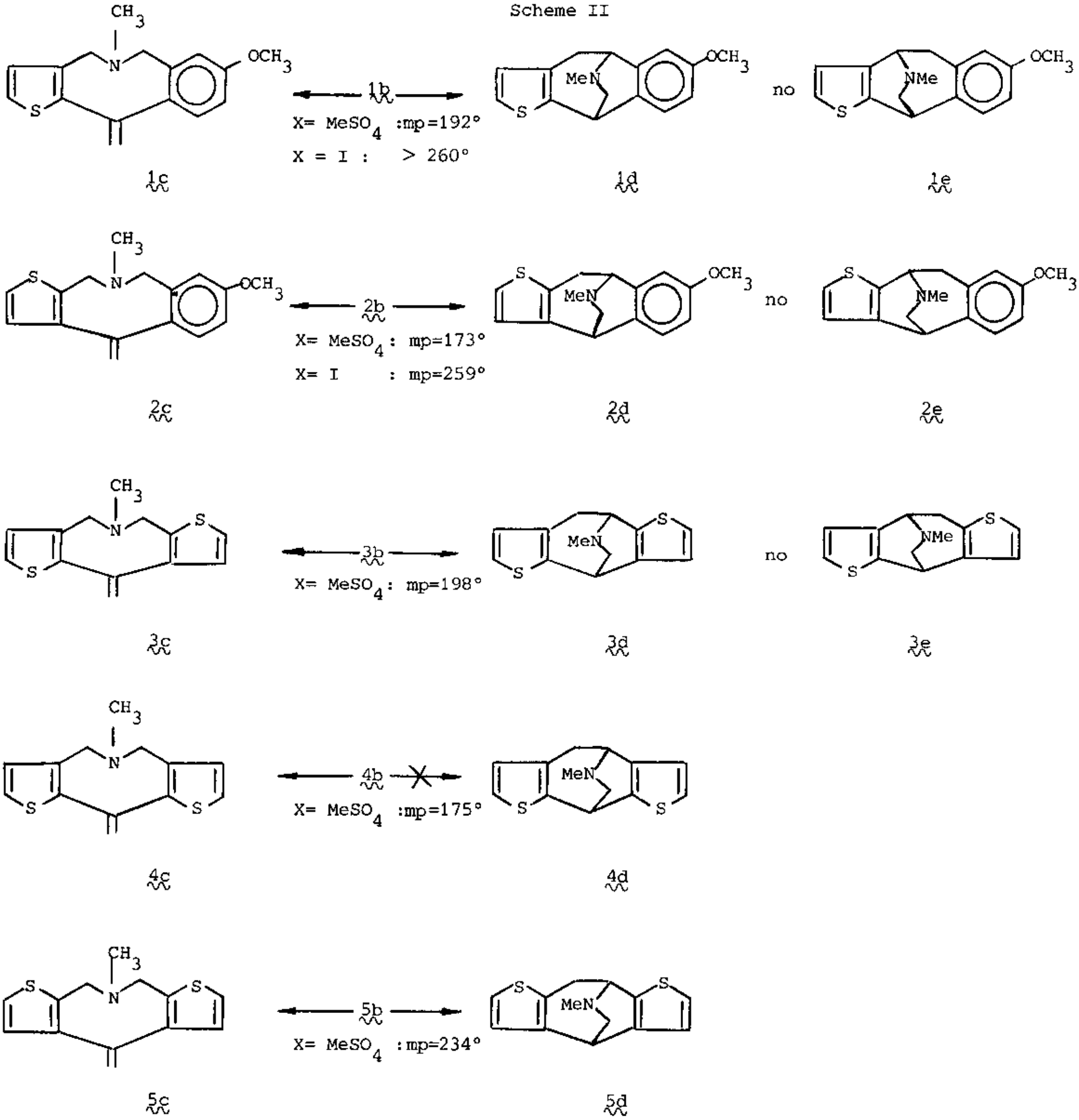
3a
3b

4a
4b

5a
5b

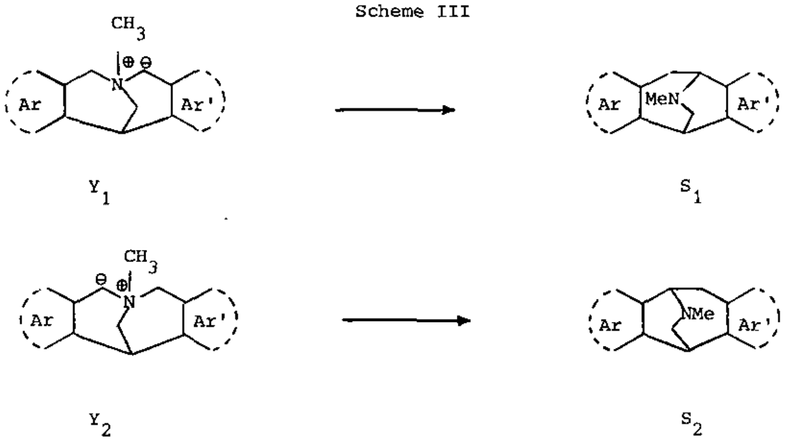
The present communication deals with the transformation, in basic medium, of the N-methyl quaternary ammonium salts (1b - 5b, R= CH_3, X= I or CH_3SO_4) obtained by treating the corresponding tertiary amines with iodomethane (1,1 eq., acetone, r.t.) or dimethylsulfate (1 eq., acetone, r.t.). The reaction regioselectivity will depend on various parameters such as the base, solvent and X-anion nature, the reaction temperature and the reagents concentrations. In fact, the geometry of the system excluding any SOMMELET's transformation[2,4] is in favour of an HOFMANN's anti-elimination[3] (Scheme 5) or in favour of a STEVENS's rearrangement[4]. Moreover, the HOFMANN's elimination

Scheme II



will give in any case a unique compound (1c - 5c)(Scheme II) while the STEVENS's rearrangement could lead to two different amines (1d - 3d) and/or (1e - 3e) from the dissymetric ammonium derivatives (1b - 3b). Indeed, two ylids Y_1 or Y_2 could be formed, each of them leading to a different rearrangement product (Scheme III). The reaction will be partly oriented according to the relative acidity of the protons involved in the basic attack.

Scheme III



RESULTS (Tables I and II)

Table I

Ratio of elimination/transposition products from methylsulfates (1b - 5b)

Methylsulfates	*50% aq.NaOH-toluene (a)*		*30 % KOH-MEOH*	
	Total Yield %	(c) Hofmann/Stevens	Total Yield %	(c) Hofmann/Stevens
1b	97	11/89	98	100/0
2b	72	0/100	58	100/0
3b	96	25/75	96	100/0
4b	98	100/0	95	100/0
5b	96	0/100	90	94/6

a) the salt (1,3 mmole) was refluxed under nitrogen atmosphere for 2 h 30 in 50 % aq. NaOH (50 cm^3) and toluene (50 cm^3).

b) the salt (1,3 mmole) was refluxed under nitrogen atmosphere for 20 h in 30 % KOH-MeOH (100 cm^3).

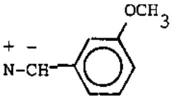
c) VPC determination.

After several tryings we arrived to the following conclusions :

The HOFMAN's elimination preferably occured in good yields when the reaction was carried out in 30 % methanolic KOH solution at reflux temperature and under nitrogen atmosphere.Similar results were obtained when iodides as well as methylsulfates were used as starting materials.

Except for 4b, the STEVENS 's rearrangement preferably took place when a refluxing 50 % aqueous NaOH-toluene biphasic system was used as reaction mixture. Indeed, by analogy with reactions carried out in heterogeneous mixtures with quaternary ammonium salts as phase transfer catalyst, we had expected that the hydroxides (1b-5b) (X = OH) which are formed in the aqueous phase, would preferentially undergo the *STEVENS's rearrangement in the quasi-anhydrous aprotic organic phase.* Moreover a unique transposition product (1d-3d) was isolated from the dissymetric ammonium salts

(1b-3b). Their structure was proved by an unequivocal synthesis process (see below). If we consider that the ylid formation is rate determining, we are thus able to range the ease of formation of these ylids in the order :


(I)

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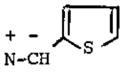
(II)

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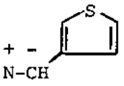
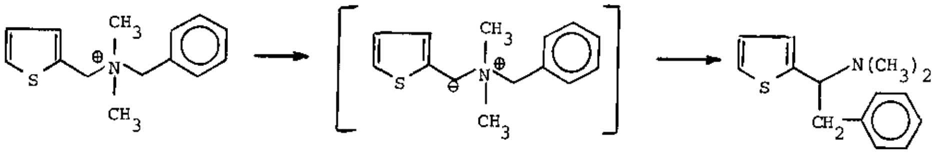

(III)

However, according to some physicochemical studies[5], the electron attractor effect of thienyl and phenyl radicals were classified as follows :

2-thienyl > phenyl ⩾ 3-thienyl

and accordingly, it was observed by A.G. GIUMANINI and C. TROMBINI[6] that the quaternary ammonium salt (6) preferably yielded the ylid (7), when treated by strong bases except sodium amide which led to a SOMMELET's transposition (Scheme IV).

Scheme IV

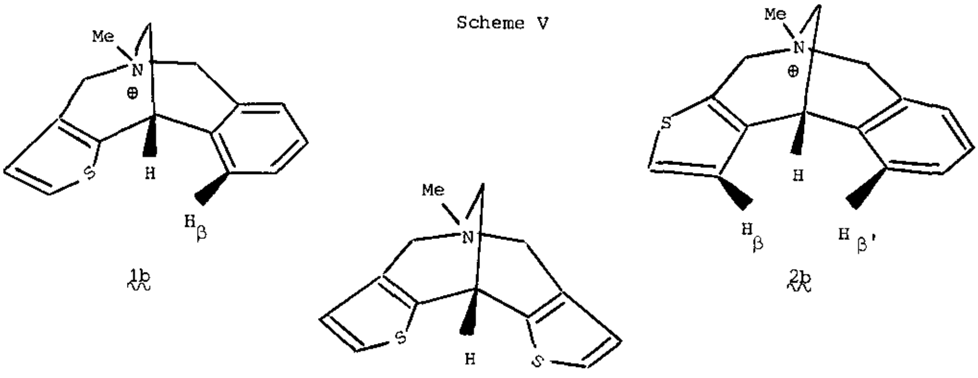


6 7 8

But, in our case the electron withdrawing effect of the meta-methoxy group ($\sigma = + 0{,}12$) may explain an easier formation of the ylid (I) rather than (II) or, *a fortiori*, (III). Nevertheless further studies would be neccesary to evaluate the weight of this substituant effect.

We have also observed that, even when the experimental conditions were in favor of the STEVENS's rearrangement, the Hofmann's elimination occurred as much easily as the involved proton is more acidic and more accessible towards the basic reagent. In fact, the access to the reactive hydrogen may be sterically hindered by the β and β' hydrogen atoms on the aromatic nucleus. For exemple, (Scheme V) compound (1b) underwent more easily an Hofmann's reaction rather than its isomer (2b), since the involved hydrogen atom is at once more acidic and less hindered.

Scheme V



1b 4b 2b

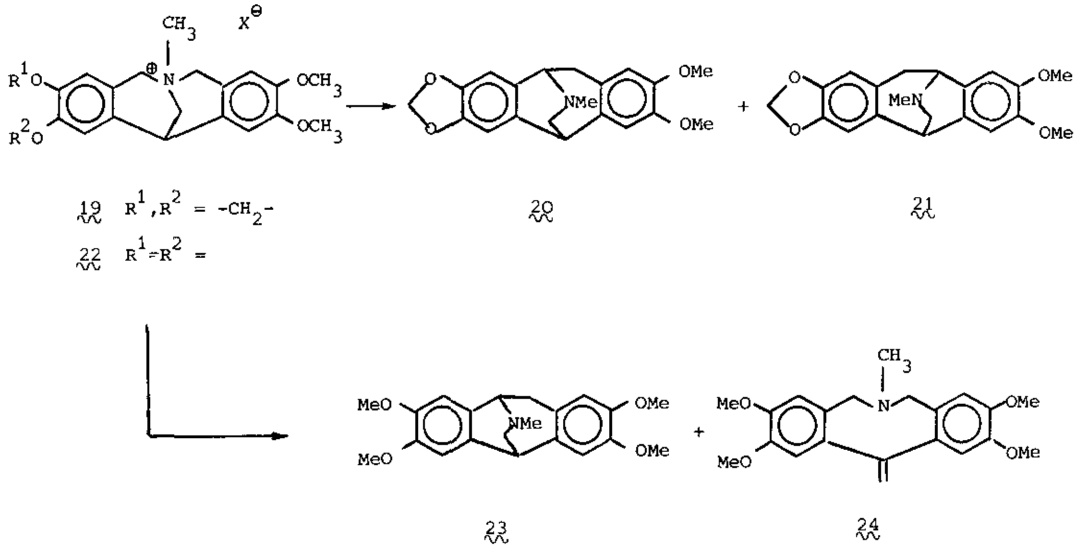
These regioselectivity factors are better exemplified by the ammonium (4b) which never underwent *any STEVEN's rearrangement.*

In general, the reaction regiospecificity was not influenced by using potassium tert-butoxide in tetrahydrofuran . In the contrary, the STEVEN's rearrangement was predominant when the reaction was carried out with butyllithium in tetrahydrofuran , but some unidentified impurities were also formed.

Otherwise, in the 50 % aq. NaOH-toluene system, yields were better when X^- was the methylsulfate anion.

Our results have to be brought together with those recently published[10] by H. TAKAYAMA and coll. By treating the asymmetrical iodide (19) with potassium tert-butoxide in tetrahydrofuran at 80°C, these authors obtained in 85 % yield a mixture of (±) amurensinine (20) and (±) reframine (21) resulting of a STEVEN's rearrangement (Scheme VI).

Scheme VI



19 R^1,R^2 = -CH$_2$-

22 R^1=R^2 =

20

21

23

24

We have also observed that a STEVEN's rearrangement and a HOFMANN's elimination simultaneously occured when the symmetrical methylsulfate (22) derived from the corresponding tetracyclic amine[11] was heated in the 50 % aq.NaOH-toluene biphasic system.Indeed (±) O-methylthalisopavine(23)[12,13] (mp= 168°C (iPr$_2$O-iPrOH)) and the dibenzo[c,f]azocine (24) (mp=119°C, hydrochloride :mp = 213°C) were respectively isolated (silica gel column chromatography) in the ratio of 95 : 5.

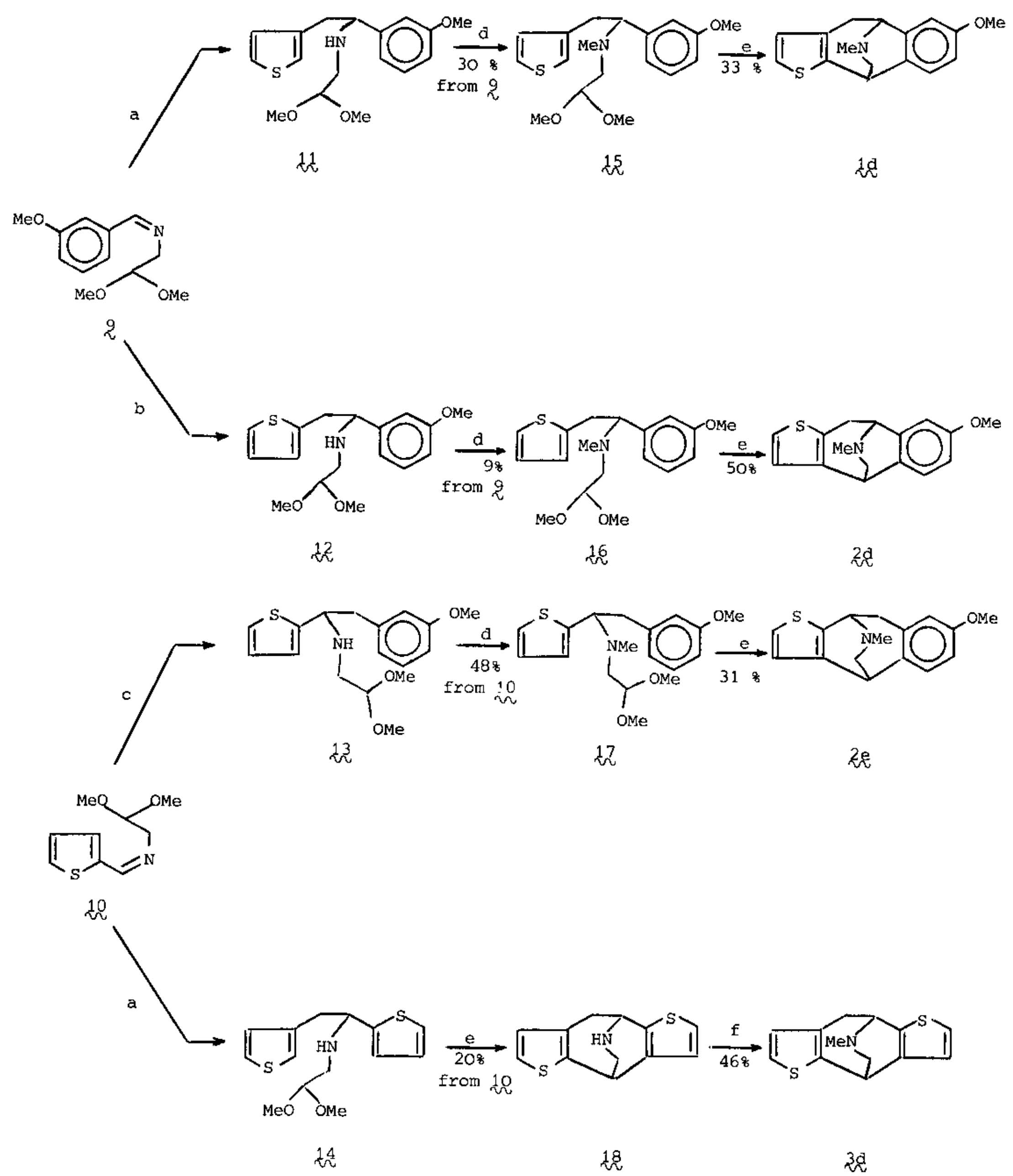
Unequivocal synthesis of amines (1d),(2d),(3d)

Since the structure of the rearrangement products (1d - 3d) could not be established by ^{1}H or ^{13}C NMR we proved it by the following unequivocal synthesis(Scheme VII).

The intermediates (11-14) were not isolated. The oily compounds (15-18) were purified by chromatography on silica gel.

The isolated final amines were found identical to the corresponding STEVENS's rearrangement products.

Scheme VII



a: 3-thenyl magnesium bromide[7], THF ; b: 2-thenyl magnesium chloride[8], EtOH ; c: m-methoxybenzyl magnesium bromide, Et_2O ; d: HCHO/MeOH reflux, then $NaBH_4$[9] ; e: 6N HCl reflux ; f: HCHO/HCOOH, reflux.

The synthesis of (2e) (mp= 81-83°C), isomer of (2d), allowed us to prove that it was not produced by STEVENS's rearrangement.

TABLE II

N°	mp°C	^{1}H-NMR δ (ppm)
1c	100-102	($CDCl_3$) 5,70(s,1H);4,90(s,1H); 3,75(s,3H); 3,40(s,2H); 3,30(s,2H); 2,25(s,3H)
2c	104-106	($CDCl_3$) 5,70(s,1H); 5,00(s,1H); 3,76(s,3H); 3,47(s,4H); 2,30(s,3H)
3c	99-101	($CDCl_3$) 6,70(d,1H,J=5Hz);5,45(s,1H); 5,25(s,1H); 3,50(s,2H); 3,30 (s,2H); 2,24(s,3H)
4c	100-102	($CDCl_3$) 7,05(d,1H,J=5Hz); 6,75(d,1H,J=5Hz); 5,35(s,2H);3,35(s,4H); 2,20(s,3H)
5c	oil	($CDCl_3$) 7,25(d,1H,J=5Hz); 7,10(d,1H,J=5Hz); 5,48(s,2H); 3,56(s,4H); 2,32(s,3H)
1d	97-98	($CDCl_3$) 3,70(s,3H); 2,45(s,3H)
2d	108-110	(C_6D_6) 3,38(s,3H); 2,29(s,3H)
2e	81-83	(C_6D_6) 3,27(s,3H); 2,20(s,3H)
3d	oil	($CDCl_3$) 6,95(d,1H,J=5Hz); 6,84(d,2H,J=5Hz); 6,10(d,1H,J=5Hz); 2,47(s,3H)
5d	125-127	($CDCl_3$) 6,72(d,1H,J=5Hz); 2,45(s,3H)
24	118-120	($CDCl_3$) 7,03(s,3H); 6,60(s,2H); 5,35(s,2H); 3,88(s,12H); 2,28(s,3H)

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