

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

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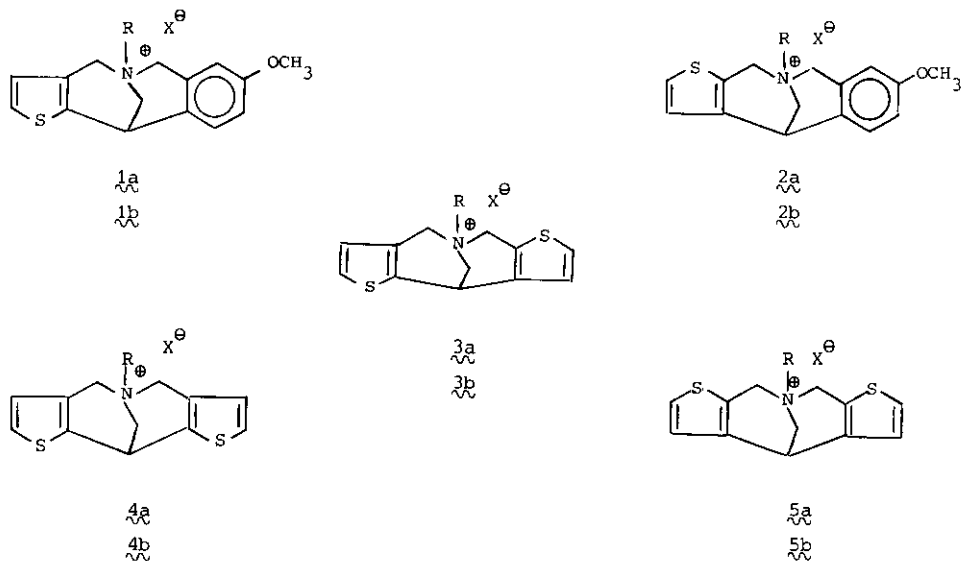
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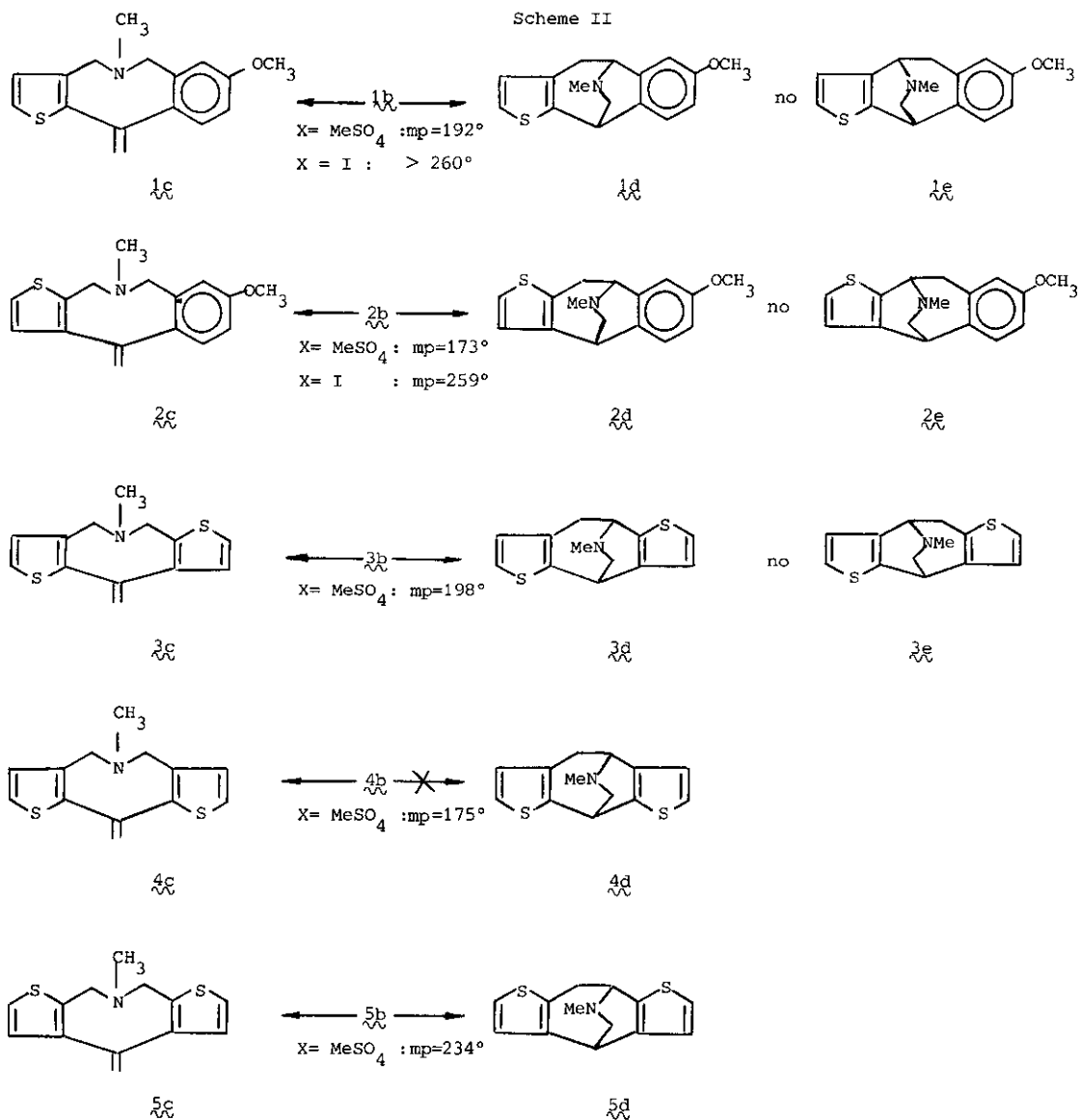
Abstract - Reactions of N-methyl quaternary salts of thiophene condensed 1-aza-bicyclo[3,3,1]nonanes with various bases were examined in order to obtain preferentially Hofman elimination or Stevens rearrangement.

In the preceding paper we reported¹ the synthesis of tetracyclic compounds (1a - 5a) (R=H, X= Cl) (Scheme I)

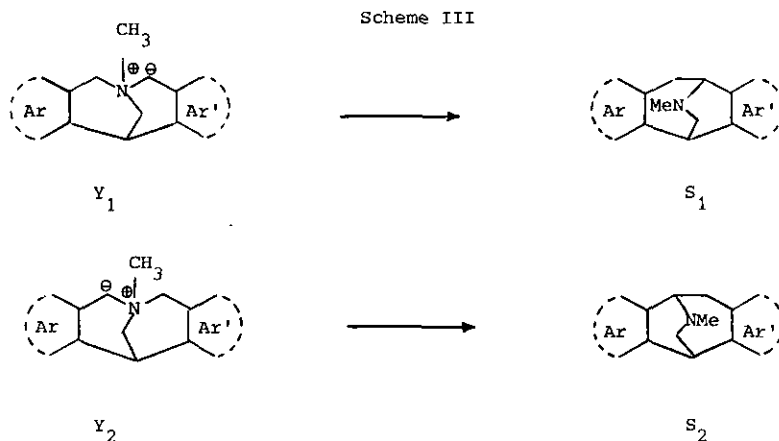
Scheme I



The present communication deals with the transformation, in basic medium, of the N-methyl quaternary ammonium salts (1b - 5b, R= CH₃, X= I or CH₃SO₄) 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-elimination³ (Scheme 5) or in favour of a STEVENS'S rearrangement⁴. Moreover, the HOFMANN'S elimination



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 dissymmetric 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.



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 %	Hofmann/Stevens (c)	Total Yield %	Hofmann/Stevens (c)
$1b$	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 cm³) and toluene (50 cm³).

b) the salt (1,3 mmole) was refluxed under nitrogen atmosphere for 20 h in 30 % KOH-MeOH (100 cm³).

c) VPC determination.

After several tryings we arrived to the following conclusions :

The HOFMAN's elimination preferably occurred 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 dissymmetric ammonium salts

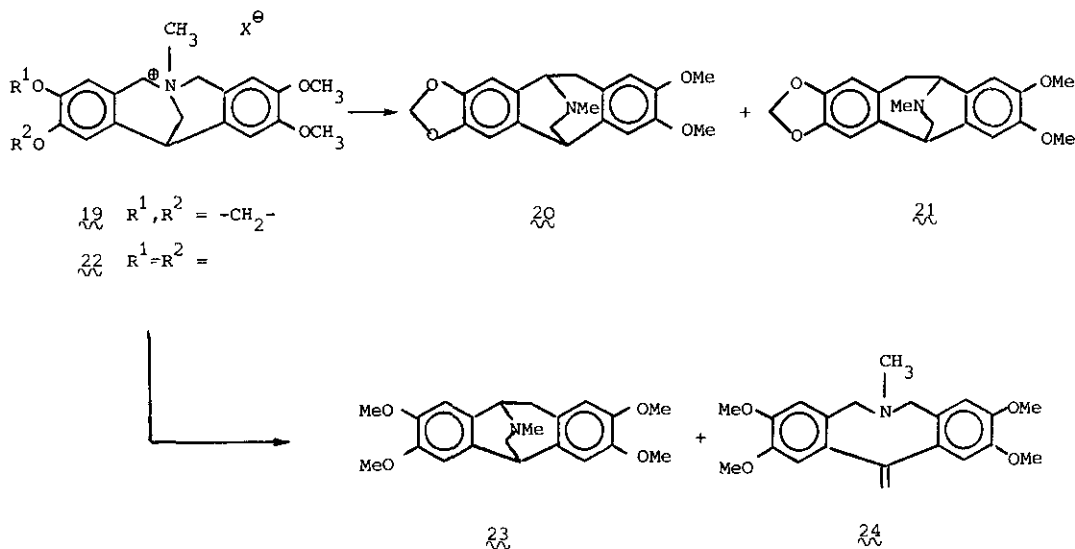
These regioselectivity factors are better exemplified by the ammonium (4b) which never underwent any STEVEN'S rearrangement.

In general, the reaction regioselectivity 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 published¹⁰ 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



We have also observed that a STEVEN'S rearrangement and a HOFMANN'S elimination simultaneously occurred when the symmetrical methylsulfate (22) derived from the corresponding tetracyclic amine¹¹ was heated in the 50 % aq. NaOH-toluene biphasic system. Indeed (+) O-methylthalisopavine (23)^{12,13} (mp = 168°C (iPr₂O-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.

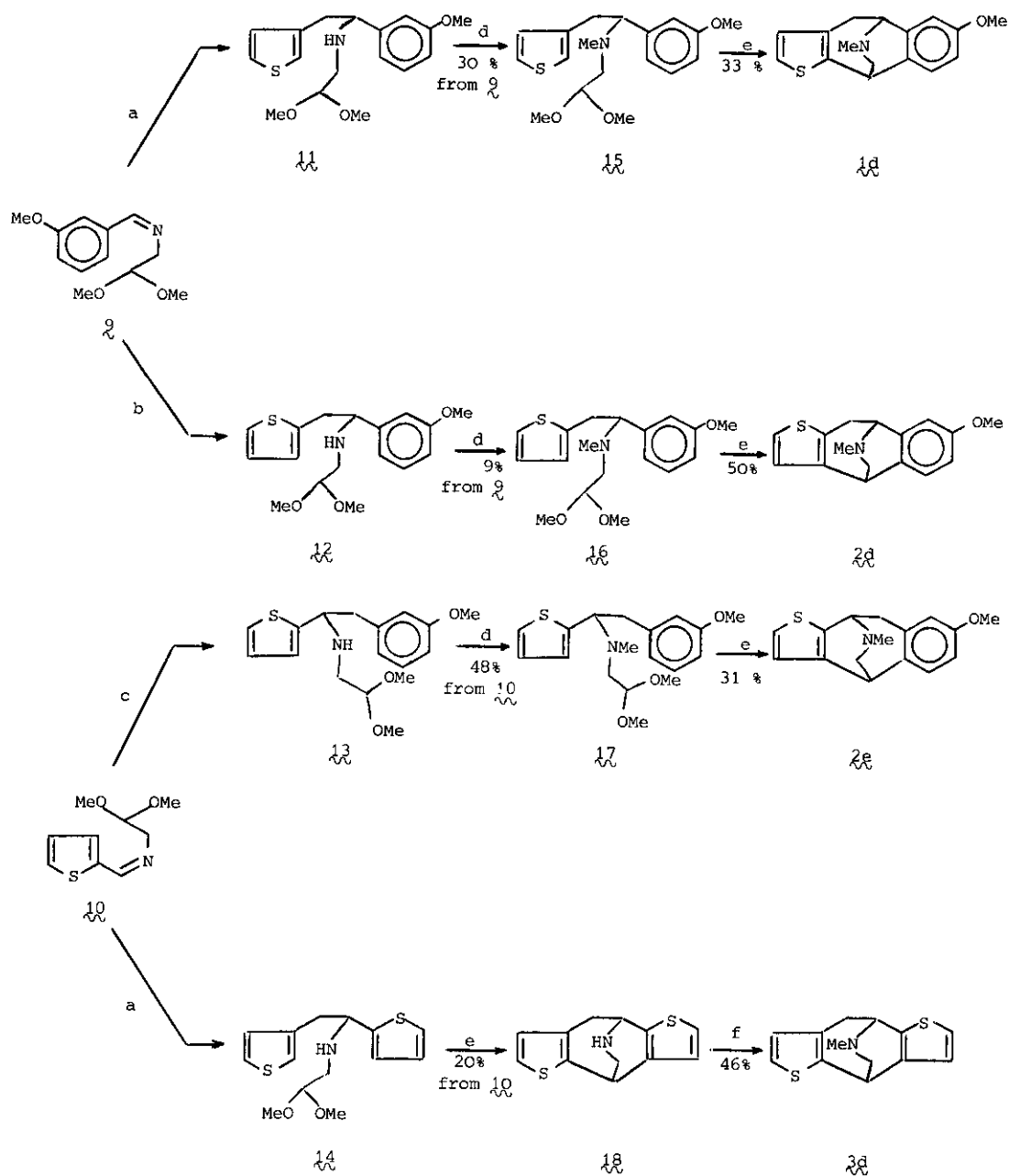
Unequivocal synthesis of amines (1a), (2a), (3a)

Since the structure of the rearrangement products (1a - 3a) could not be established by ¹H or ¹³C 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 STEVEN'S rearrangement products.

Scheme VII



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)
1e	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)
2e	104-106	(CDCl ₃) 5,70 (s,1H); 5,00 (s,1H); 3,76 (s,3H); 3,47 (s,4H); 2,30 (s,3H)
3e	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)
4e	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)
5e	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 ₆ D ₆) 3,38 (s,3H); 2,29 (s,3H)
2e	81-83	(C ₆ D 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)
2d	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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