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CONFORMATIONAL AND STERIC REQUIREMENTS OF THE SIDE CHAIN FOR SULPHUR PARTICIPATION IN BENZTHIEPIN DERIVATIVES

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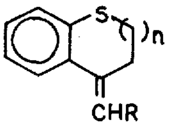
Abstract : Attempted ring expansion of some benzthiepin derivatives resulted in the formation of benzthiophens such as (3a,b) and (3d,e). A probable mechanism for this transformation has been presented.

In connection with some other problems, we required the thiooctalone derivative (2a) in quantity. The obvious choice for the preparation of (2a) was through the ring expansion of easily available 5-methylene-2,3,4,5-tetrahydro-1-benzothiepin (1a). We report here an interesting intramolecular S-participation in our attempted ring expansion of (1a-b) leading to 1-benzothiophens (3a-g) of current interest[1].

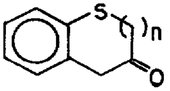
The exo-methylene compounds (1a), δ 5.20 (1H,d,J 2Hz) and (1b)[2] were available through Wittig reactions of homothiachromanone with appropriate phosphoranes. Heating under reflux a methanolic solution of (1a) and $AgNO_3$ in the presence of iodine as prescribed[3] for ring expansion of the related 6-membered carbocyclic ring, afforded a water soluble material(s) showing no i.r. absorption in the carbonyl region[4]. Hydrolysis of this material with alcoholic HCl furnished, interestingly, the benzthiophen derivative (3a) as the only isolable product (58%), m/z doublet at 210 and 212 (M^+); special features of ^1H n.m.r. spectrum : δ 7.18 (1H,s), 3.62 (2H,t, J 8Hz), 3.06 (2H,t,J 7Hz) and 2.23 (2H,m). The structure (3a) was unambiguously established through its conversion to the known crystalline acid (3c)[5] in excellent yield. The ethylidene derivative (1b) similarly afforded in relatively lower yield (25%) the benzthiophen derivative (3b), the salient features of its ^1H n.m.r. spectrum are the two triplets at δ 3.50 (2H,J 7Hz) and 2.94 (2H,J 7Hz), and a singlet at 2.48 (3H).

Attempted ring expansion of (1a) with thallium nitrate[6] in methanol gave again a water soluble material which on hydrolysis as before provided (3a) in moderate yield (37%). It is interesting to note that the related thiachroman derivative (1c) by the above procedure (TTN-MeOH afforded[6] in excellent yield the desired ring expansion product (2b).

The mechanism shown in the Scheme 1 may be proposed for the transformation of (1a,b) to (3a,b). A Dreiding model reveals axial conformation (A) of the side chain ($-CH_2-X$ in the Scheme)



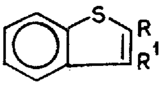
(1)	n	R
a	2	H
b	2	Me
c	1	H



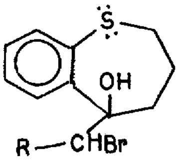
(2)

a; n = 3

b; n = 1



(3)	R	R^1
a	H	$[CH_2]_3Cl$
b	Me	$[CH_2]_3Cl$
c	H	$[CH_2]_3CO_2H$
d	H	$[CH_2]_3Br$
e	Me	$[CH_2]_3Br$
f	Me	$[CH_2]_3CO_2H$
g	$[CH_2]_2CO_2H$	Me

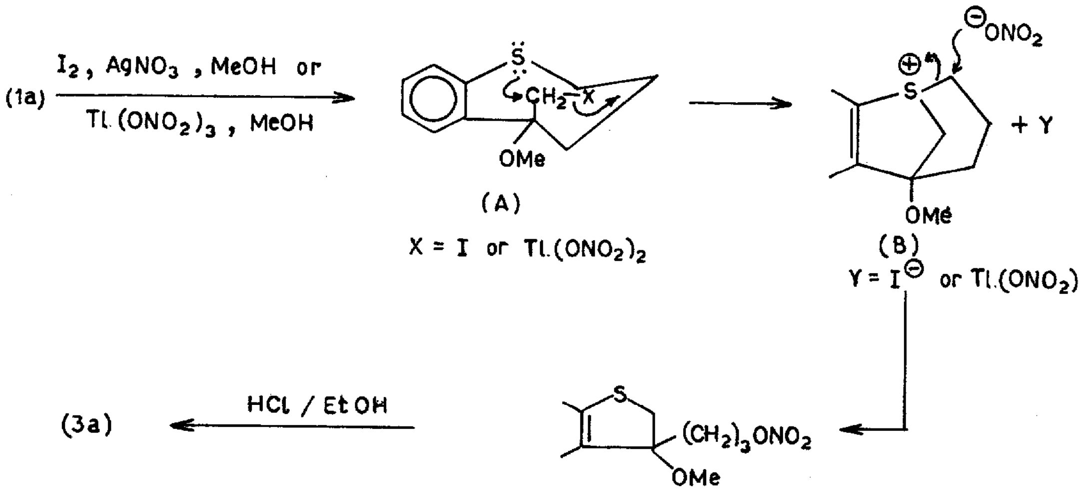


(4)

a; R = H

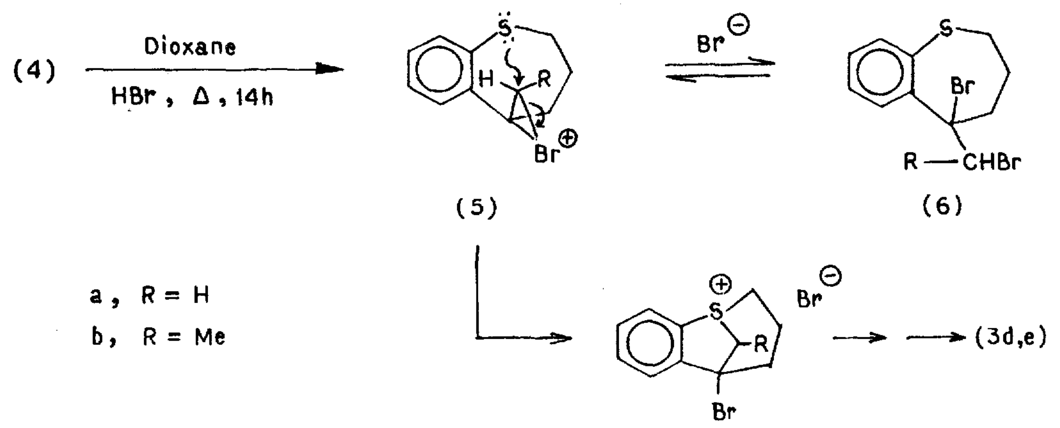
b; R = Me

for effective S-participation leading to the bicyclo[3.2.1]octane intermediate (B). Steric considerations of the side chain seem to play a vital role on the ease of S-participation.



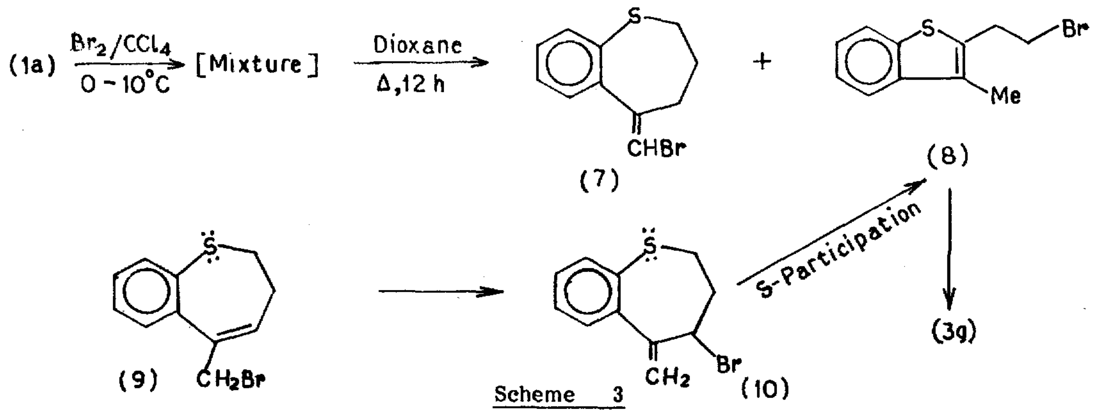
Scheme 1

The above mechanism (Scheme 1) probably gets support from the following observations. Heating under reflux (12h) a solution of the crystalline bromohydrin (4a)[7] in dry dioxane containing a few drops of HBr (48%) afforded, interestingly, the benzthiophen derivative (3d) in good yield (63%). The crystalline bromohydrin (4b)[7] similarly provided the expected benzthiophen (3e) in comparable yield (64%). The ^{1}H n.m.r. spectra of (3d,e) are similar to the corresponding chloro-derivatives (3a,b) reported earlier. The above bromide (3e) was finally converted in near quantitative yield to the crystalline acid (3f), δ 2.86 (2H,t,J 7Hz), 2.48 (3H,s), 2.42 (2H,t,J 7Hz) and 2.16-1.84 (2H,m). It may be mentioned that the above bromohydrin (4a) on heating under reflux (22h) simply in dry dioxane gave in very low yield (19%) the benzthiophen (3a) mentioned above. The efficient transformation of the bromohydrins (4a,b) to benzthiophens (3d,e) in the presence of HBr probably *suggests S-participation on the very reactive* *spiro-bromonium ions* (5a,b) in equilibrium with the dibromides (6a,b) as shown in the Scheme 2.



Scheme 2

Attempted preparation of the above dibromide (6a) by addition of bromine to (1a) under mild condition provided a complex mixture[8] (Scheme 3). Heating under reflux (12h) a solution



Scheme 3

of this mixture in dry dioxane furnished a ca. 7:3 mixture[9] (from g.l.c.) of the vinyl bromide (7) and the banzthiophen derivative (8) respectively. This mixture on treatment with KCN in DMSO followed by alkaline hydrolysis afforded a separable mixture of the crystalline acid (3g), δ 3.27 (2H,t,J 7Hz), 2.80 (2H,t,J 7Hz) and 2.39 (3H,s); and the pure vinyl bromide (7), m/z doublet at 254 and 256 (M^+); δ 6.39 (1H,s), 3.04-2.76 (4H,m) and 2.30-2.04 (2H,m). The benzthiophen derivative (8) probably originates through S-participation on the allylic bromide (10) formed as a result of rearrangement of the isomeric bromide (9) present in the original mixture as depicted in Scheme 3.

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4. The exo-methylene compounds prepared from benzsuberone and homochromanone derivatives provided in moderate yields the expected ring-expanded ketones (our unpublished work) under this condition ($AgNO_3$-I_2 in MeOH).
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7. The bromohydrins (4a) and (4b) were prepared from (1a) and (1b) respectively following essentially the procedure of Dalton et al, J. Am. Chem. Soc., **90**, 5498 (1968).
8. ^{1}H n.m.r. spectrum (200 MHz) of this mixture revealed mainly the presence of the vinyl bromide (7) and the allylic bromide (9), and a small amount of the benzthiophen derivative (8).
9. This mixture could not be separated by careful chromatography over silica gel or alumina.

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