SYNTHESES AND REARRANGEMENTS OF SOME FOUR-MEMBERED HETEROCYCLIC COMPOUNDS+

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SUMMARY

Acid catalysed cyclodehydrations of n-(β-phenylmercapto)-propyl phenyl ketone 9 and β-phenyl-β-phenylmercaptoethyl methyl ketone 10 led to the mixture of 2-methyl-4-phenyl-thianaphthalenium perchlorate 11 and 4-methyl-2-phenyl-thianaphthalenium perchlorate 12 along with cis (A) and trans (B) mixture of 2-methyl-4-phenylthiachroman 13 and 4-methyl-2-phenylthiachroman 14 in varying proportion. The formation of rearranged products 12 and 14 from 9 and that of 11 and 13 from 10 is rationalised by postulating the formation of 1-S-phenyl-1-thioniumcyclobut-2-ene perchlorates 15 and 16 as the reactive intermediates. These intermediates, along

with a few analogues such as 17, 18 and 19, were synthesised and some of their rearrangement reactions were studied. On the same lines, acid catalysed cyclodehydrations of 1-phenylmercapto-1-phenylbutan-2-ol 31/34 and 3-phenylmercapto-1-phenylbutan-1-ol 32/33, respectively prepared by two different methods, gave a mixture of cis and trans stereoisomers of 13 and 14 in varying proportions. The rearrangement reactions, observed during the above cyclodehydrations, have been explained by envisaging the formation of an intermediate such as 1-S-phenyl-1-thioniumcyclobutane perchlorate 36. However its synthesis has not yet been successful.

Acid catalysed cyclodehydration of 1-arylamino-3-alkanols also gave a mixture of normally expected 3,4-disubstituted 1,2,3,4-tetrahydroquinolines as well as 2,3-disubstituted-1,2,3,4-tetrahydroquinolines. Thus the cyclodehydration of 3-(3'-methoxyphenyl)amino-1-phenylbutan-1-ol 38, prepared by two alternate methods gave the rearranged tetrahydroquinoline 40B and 1-(3'-methoxyphenyl)amino-1-phenylbutan-3-ol 39B , prepared by the reduction of enaminoketone such as 42 gave a mixture rearranged tetrahydroquinolines 43A and 43B and the normally expected tetrahydroquinoline 40A. On the contrary, 1-(3'-methoxyphenyl)amino-1-phenylbutan-3-ol (39A - a stereoisomer of 39B) prepared by the reduction of β-arylamino ketone 41 gave only unrearranged tetrahydroquinoline 40A. In these series also, the formation of rearranged tetrahydroquino-

lines has been explained by the intermediacy of N-aryl-azetidines. A number of N-arylazetidines were prepared from the corresponding 1-arylamino-3-alkanols and their rearrangements to 1,2,3,4-tetrahydroquinoline under acidic conditions were studied. A more stereoselective synthesis of 2,4-disubstituted N-arylazetidines such as 46A and 46B has also been achieved.

Acid catalysed cyclodehydration of β-phenylmercapto-ethyl alkyl/cycloalkyl/aryl ketones 1 leads to the formation of thianaphthalenium salts 2 and thiachromans 3. The keto-sulphides, on acid treatment, furnish the intermediate Δ^3-thiachromene 4 which immediately undergoes disproportionation *in situ* by intermolecular hydride transfer to yield 2 and 3[1,2]. Analogously, the formation of quinoline derivatives 5 and the corresponding 1,2,3,4-tetrahydro-quinolines 6 by cyclodehydration of β-phenylaminoethyl alkyl/cycloalkyl/aryl ketones 7 has also been explained by the formation of the intermediate 1,2-dihydroquinoline 8 and its subsequent disproportionation[3]. This mechanism was substantiated by the independent synthesis of 4 and 8 and a study of their disproportionation under identical conditions and also by deuterium incorporation studies[4].

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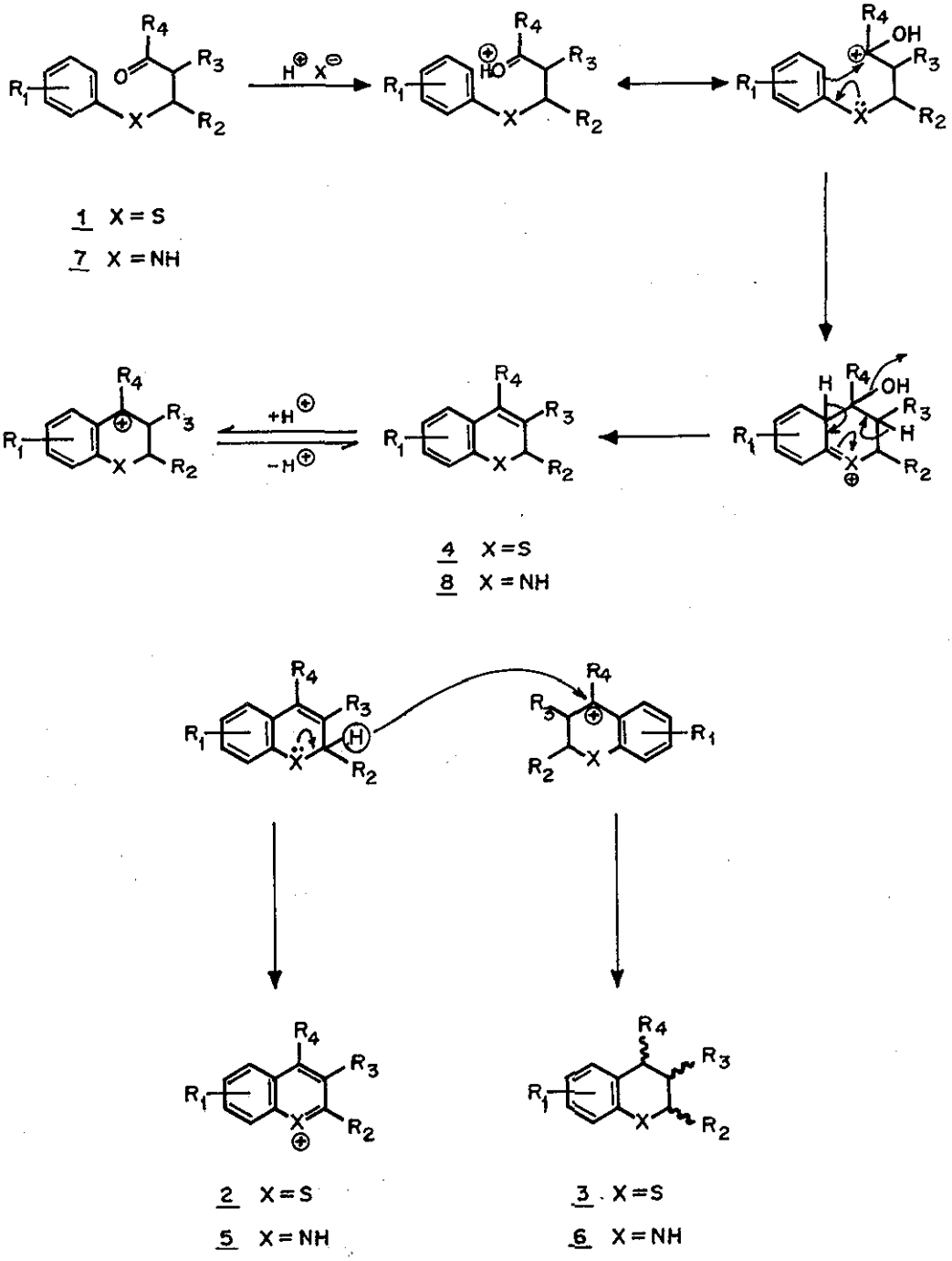
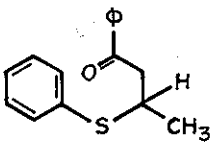


CHART — 1 .

Careful reexamination of the perchloric acid catalysed cyclodehydration products of n-(β-phenylmercapto)-propyl phenyl ketone 9 and β-phenyl-β-phenylmercaptoethyl methyl ketone 10 revealed that in both these reactions a mixture of 2-methyl-4-phenylthianaphthalenium perchlorate 11 and 4-methyl-2-phenylthianaphthalenium perchlorate 12 was obtained along with cis (A) and trans (B) mixture of 2-methyl-4-phenylthiachroman 13 and 4-methyl-2-phenylthiachroman 14 in varying proportion. Whereas the formation of 11 and 13 (A and B) from 9 and that of 12 and 14 (A and B) from 10 proceeds normally as shown in Chart 1, the formation of 12 and 14 (A and B) from 9 and that of 11 and 13 (A and B) from 10 can be rationalised by postulating the intermediate formation of 1-S-phenyl-1-thioniumcyclobut-2-ene perchlorates 15 and 16[5].

To confirm the involvement of the above four-membered sulphur heterocyclics 15 and 16 in the above cyclodehydration, their independent synthesis was necessary. Thus when n-(β-phenylmercapto)propyl phenyl ketone 9 was reacted with phosphorus oxychloride and then treated with 70% perchloric acid, 4-methyl-2-phenyl-1-S-phenyl-1-thioniumcyclobut-2-ene perchlorate 15 was obtained. Analogously 2-methyl-4-phenyl-1-S-phenyl-1-thioniumcyclobut-2-ene perchlorate 16, 2,4-diphenyl-1-S-phenyl-1-thioniumcyclobut-2-ene perchlorate 17, 2-p-methoxyphenyl-



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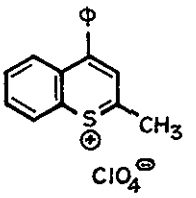

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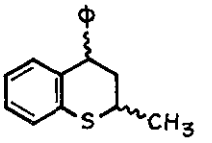
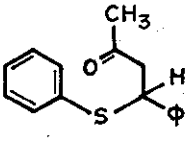


13 A, B



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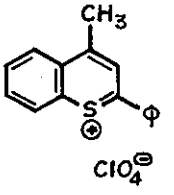

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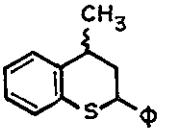
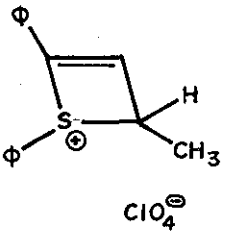


14 A, B

A : Φ , CH_3 — cis

B : Φ , CH_3 — trans



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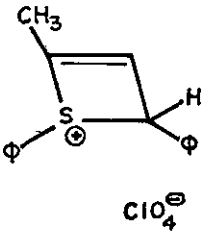


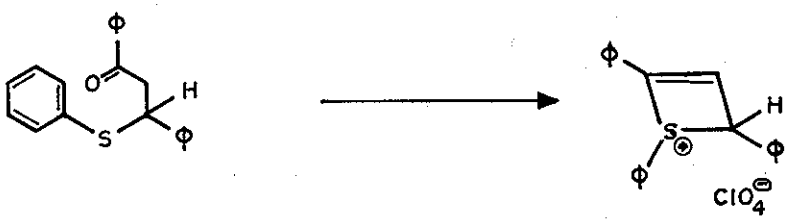
16

CHART -2.

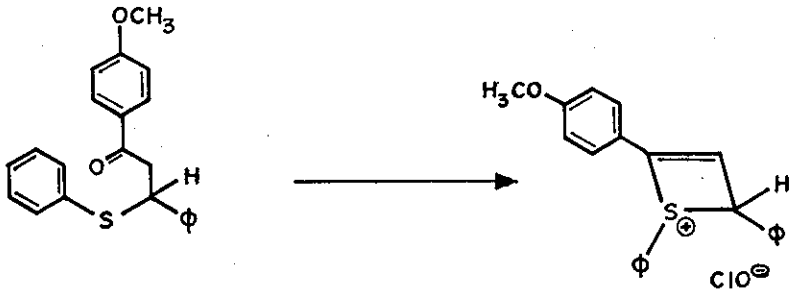
4-phenyl-1-S-phenyl-1-thioniumcyclobut-2-ene perchlorate 18 and 4-p-methoxyphenyl-2-phenyl-1-S-phenyl-1-thioniumcyclobut-2-ene perchlorate 19 were prepared by interacting 10, β-phenyl-β-phenylmercaptoethyl phenyl ketone 20, β-mercaptophenyl-β-phenylethyl p-methoxyphenyl ketone 21[6] and β-p-methoxyphenyl-β-phenylmercapto ethyl phenyl ketone 22 respectively.[6]

On warming with 70% perchloric acid, 15 rearranged to a pair of thianaphthalenium perchlorates 11 and 12 and a pair of thiachromans 13 and 14. The formation of these compounds probably occurs through double bond migration in 15 to give the isomeric perchlorate 16. Compounds 15 and 16 then lead to 11, 12, 13 and 14 via the intermediate Δ^2-thiachromenes 23 and 24 respectively. The perchlorate 16, however, on warming gave only 11 and 13 presumably through Δ^2-thiachromene 24. The change of 15 into 16 in perchloric acid was studied by monitoring the PMR spectrum during the reaction and studying the methyl signal. Under identical conditions 16 does not equilibrate with 15.[5]

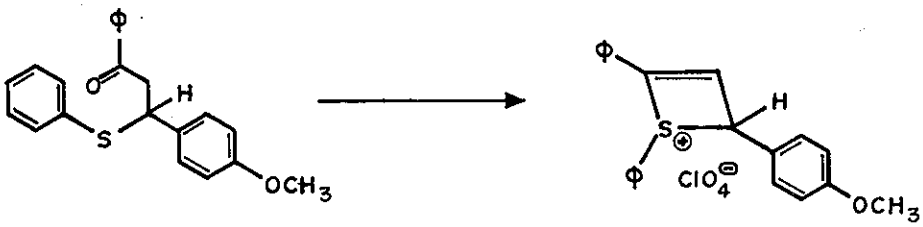
Compound 15 was also converted into 16 in another interesting manner by proton abstraction from 15 with sodium hydride in tetrahydrofuran and diethyl ether followed by reprotonation. In this process the yellow coloured 10 was converted into a deep olive green coloured



20 17



21 18



22 19

CHART -3.

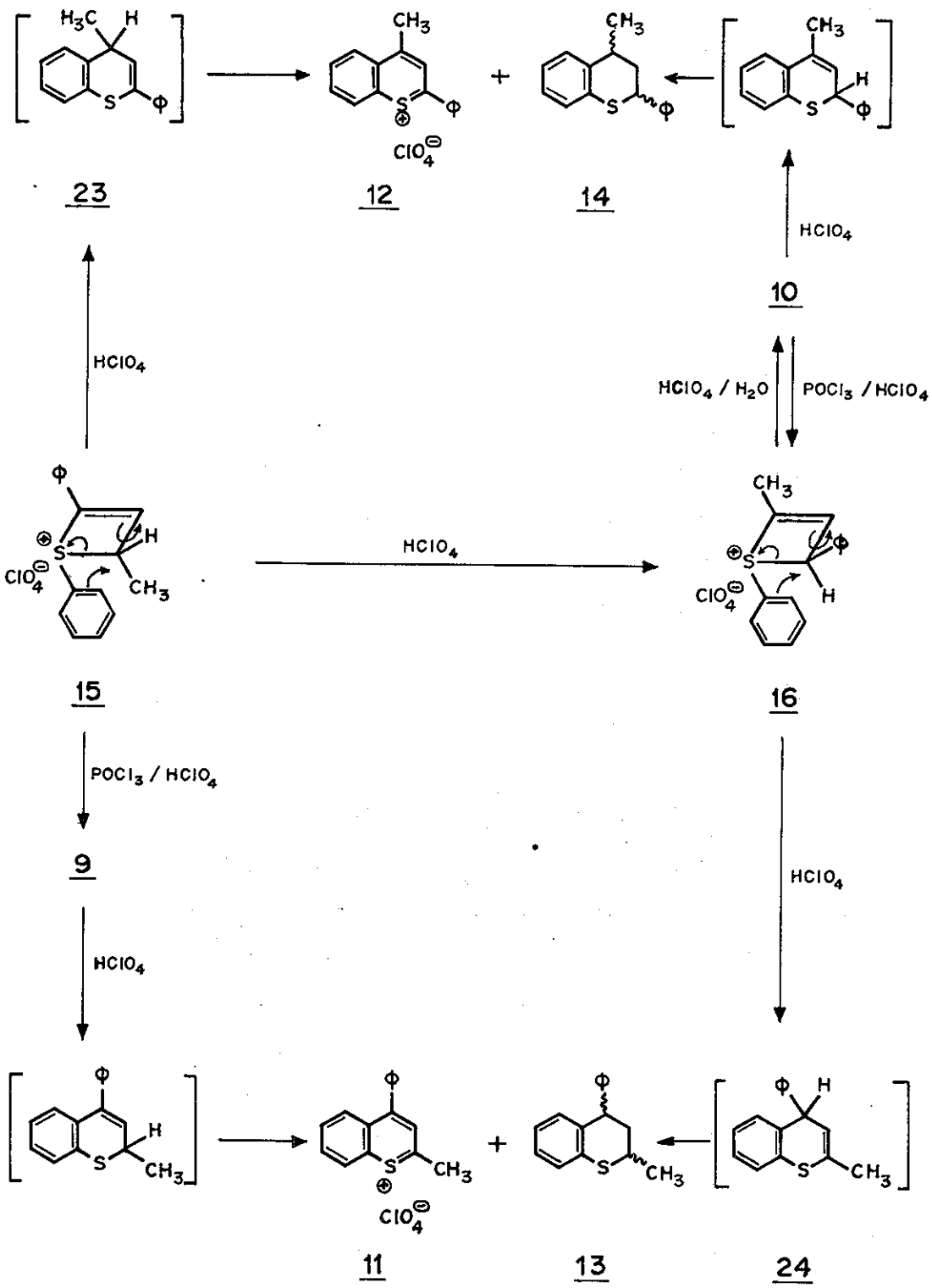


CHART – 4 .

product which appears to be 2-methyl-4-phenyl-1-S-phenyl-1-thiacyclobutadiene (25, 26). The formation of 16 on reprotonation, indicates the dominance of the dipolar form 26A as compared to 25A. Compound 16, on similar treatment with sodium hydride gave thiacyclobutadiene (25, 26) which on protonation gave back only 16. Among the various resonance forms 25, 26, 25A and 26A for the olive green coloured sulphur heterocyclic compound, the dipolar form 26A obviously dominates over others.[5]

Yet another explanation to account for the formation of 11, 12, 13 and 14 from 9 can be put forth. In acidic medium 15 may be getting converted into 9 or 10 (via 16) which may then undergo cyclodehydration normally as depicted in Chart 1. It was indeed found to be the case, since 15 on treatment with water containing a few drops of perchloric acid, gave a mixture of 9 and 10 in which 10 predominated. Under similar conditions 16 gave only 10, again indicating the greater stability of 10.[5]

The acid catalysed ring opening leading to the formation of ketosulphides was also observed when perchlorates 18 and 19 were treated with water. In both the cases ketosulphide 21 was formed predominantly. However conversion of 19 into 18 could not be achieved through the intermediate formation of thiacyclobutadiene

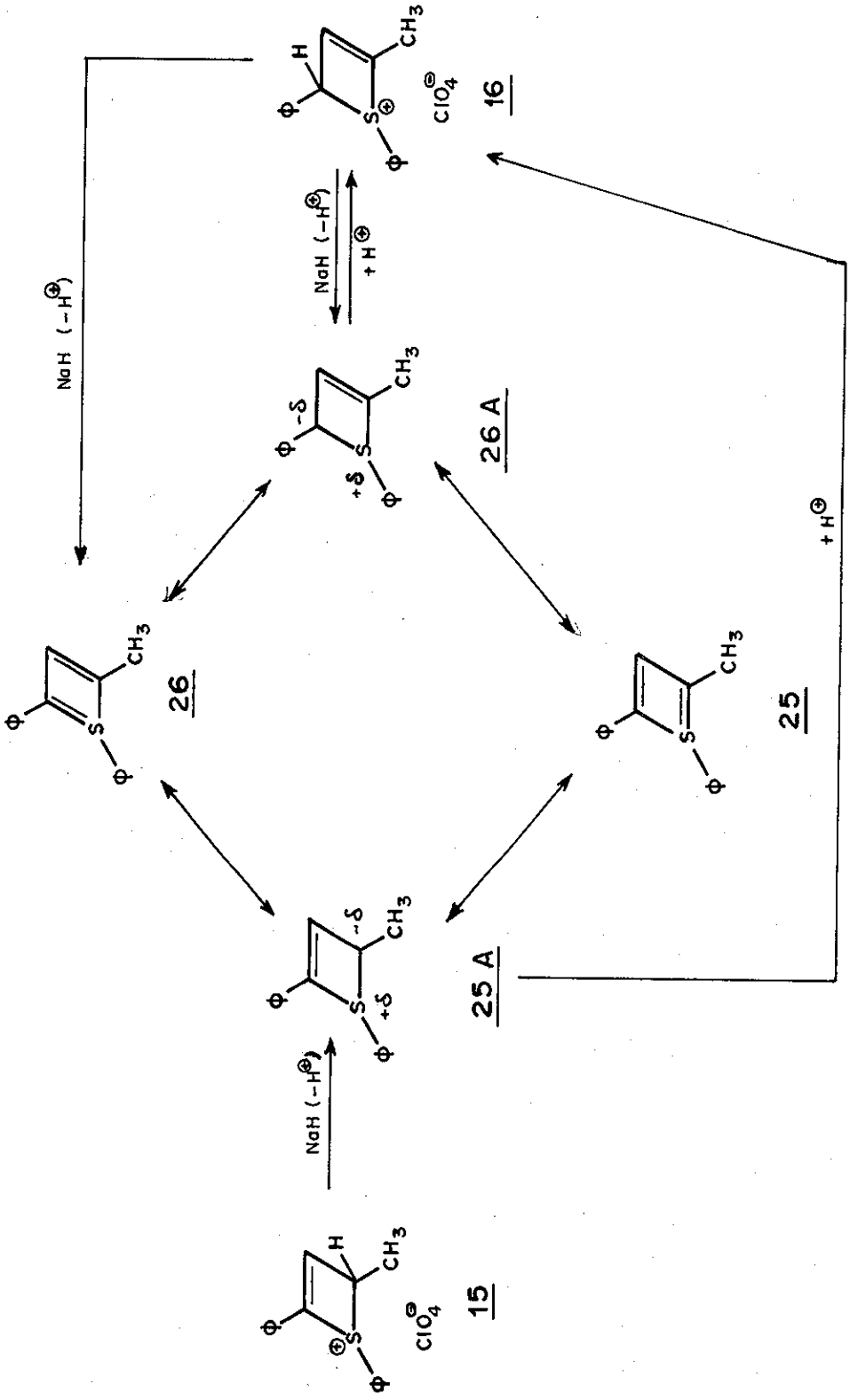


CHART-5.

and its reprotonation, because in the thiacyclobutadiene formation, both the reactions yielded only polymeric compounds.[6] These observations support the ylid structures 25A, 26A for the thiacyclobutadiene.

The mechanism of the cyclodehydration of ketosulphides indicates that the yields of the aromatic and the tetrahydro components can never individually exceed above 50%. The yields of the aromatic component increases considerably if an external hydride abstractor such as trityl chloride is incorporated during the cyclodehydration of ketosulphides.[7] For the synthesis of tetrahydro components, carbinols derived from the relevant ketosulphides were used for the cyclodehydration reaction.

A mixture of β-phenylmercaptocrotonophenone 27 and α-phenylmercaptostyryl methyl ketone 28 obtained by the condensation of thiophenol 29 and benzoylacetone 30 was reduced with sodium borohydride and the mixture of 1-phenylmercapto-1-phenylbutan-3-ol 31 and 3-phenylmercapto-1-phenylbutan-1-ol 32 was separated by column chromatography. Treatment of 31 with 70% perchloric acid gave a mixture of trans-2-methyl-4-phenylthiachroman 13B (5%) and trans-4-methyl-2-phenylthiachroman 14B (95%). Similar treatment of 32 with perchloric acid resulted in a mixture of 13B (79%) and cis 2-methyl-4-phenylthiachroman 13A (21%). Carbinol 33 prepared by

the sodium borohydride reduction of the ketosulphide 9, on treatment with perchloric acid, gave a mixture of 13A (11%) and 13B (89%). However, carbinol 34, obtained by the reduction of the ketosulphide 10, under identical conditions gave a mixture of 13A (20%) and 13B (80%).

Thus in the above set of reactions, it was observed that the cyclodehydration of the carbinols 32 and 33 led to the normally expected products 13A and 13B in more or less the same proportions. Thus these two carbinols, obtained by two different routes appear configurationally the same. On the other hand, carbinols 31 and 34 appear to be configurationally different because, under identical conditions the pattern of their cyclodehydration products are different.

The formation of the normal products such as 13A and 13B in the cyclodehydrations of carbinols 32 and 33 and that of 14B in the cyclodehydration of 31 is explained by the mechanism shown in Chart 7. However in all these cyclisations, whether leading to the normal or rearranged products, a preferential formation of the trans isomers such as 13B and 14B was observed. If the carbonium ion derived from 35 (Chart 6) is formed prior to cyclisa-

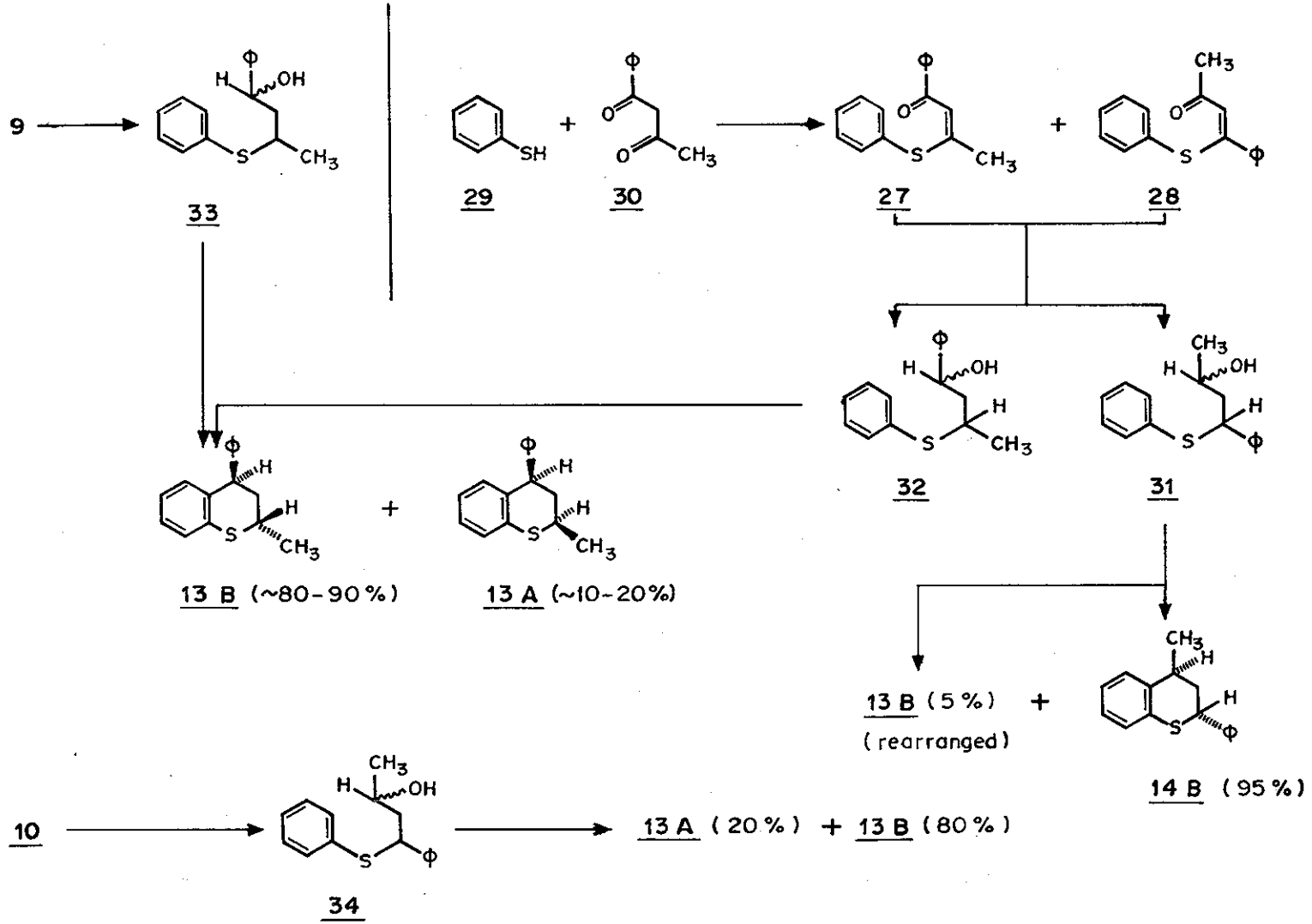

9
33
29
30
27
28
32
31
13 B (~80-90 %)
13 A (~10-20%)
13 B (5 %)
(rearranged)
14 B (95 %)
10
34
13 A (20 %) + 13 B (80 %)

CHART - 6.

tion, it can be attacked from above or below the plane carrying the carbonium ion, leading to the possibility of the formation of both cis (A) and trans (B) isomers in equal proportions.

The above cyclodehydration reactions, therefore, appear to be largely stereospecific involving concerted reactions in which discrete carbonium ions are probably not formed. The stereospecific formation of various thiachromans may be explained by involving the intermediate formation of 1-S-phenyl-1-thioniumcyclobutane perchlorates 36. The latter may then cleave in two alternate ways to yield either the normal or the rearranged products. The formation of products 13A and 13B will involve the cleavage of $\overset{\oplus}{S}-\overset{|}{C}-\phi$ bond (Route A) and that of 14A and 14B, will involve the cleavage of $\overset{\oplus}{S}-\overset{|}{C}-CH_3$ bond (Route B) in the 2-methyl-4-phenyl-1-S-phenyl-1-thioniumcyclobutene perchlorate 37 which is the likely intermediate in all these reactions. In these rearrangements Route A appears to be more facile than Route B.[8]

Attempts to synthesize 1-S-phenyl-1-thioniumcyclobutane salts such as 36 have not been successful so far.

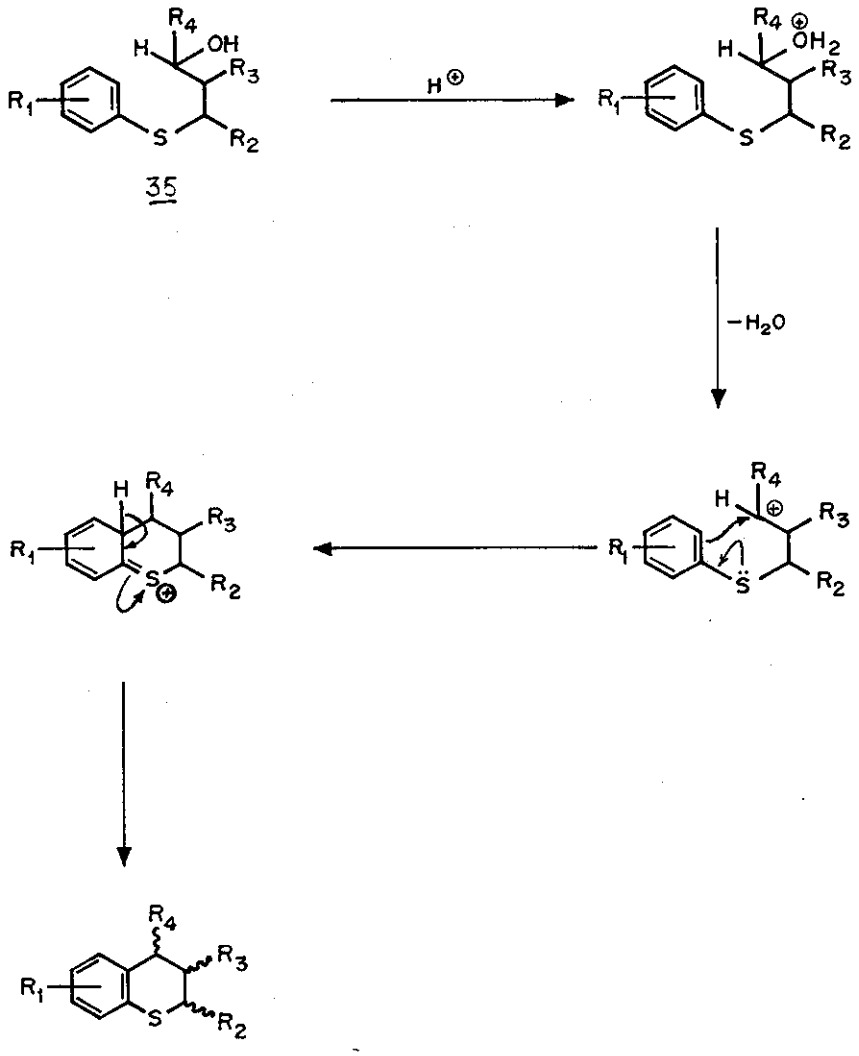
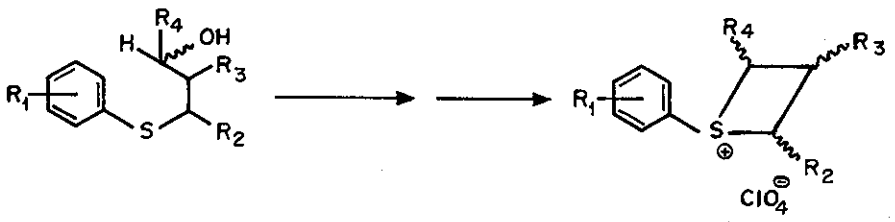


CHART -7.



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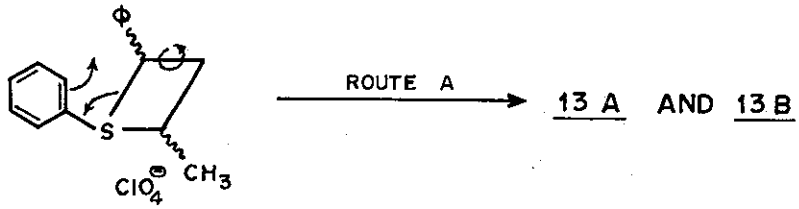

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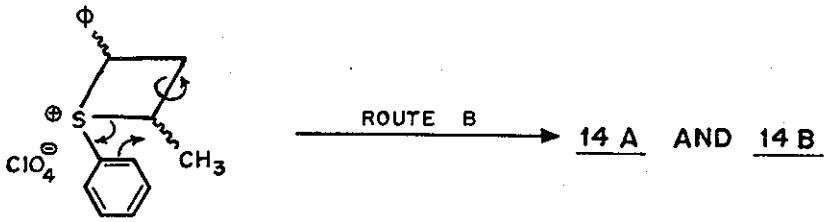


37

CHART - 8 .

As mentioned earlier, acid catalysed cyclodehydration of β-arylaminoethyl alkyl/cycloalkyl/aryl ketones leads to the formation of quinolines and corresponding 1,2,3,4-tetrahydroquinolines in equimolecular amounts.[3] For the synthesis of tetrahydroquinolines, acid catalysed cyclodehydration of 1-arylamino-3-alkanols was studied.[9] Cyclodehydration of a number of such alkanols yielded a mixture of the normally expected 3,4-disubstituted 1,2,3,4-tetrahydroquinolines as well as 2,3-disubstituted-1,2,3,4-tetrahydroquinolines which were formed by rearrangement. With a view to study these rearrangement reactions cyclodehydration of 3-(3'-methoxyphenyl)amino-1-phenylbutan-1-ol 38 and 1-(3'-methoxyphenyl)amino-1-phenylbutan-3-ol 39 was examined.[11]

The carbinol 38, prepared by two alternate methods shown in Chart 9 gave, on cyclodehydration, exclusively the rearranged product, trans-7-methoxy 4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 40B. On the other hand, carbinol 39A, prepared by reduction of β-(3'-methoxyphenyl)amino-β-phenylethyl methyl ketone 41, on cyclodehydration, gave exclusively the normal product, cis-7-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 40A, whereas the carbinol 39B, prepared by the reduction of α-(3'-methoxyphenyl)aminostyryl methyl ketone 42, on cyclodehydration yielded a mixture of the normal

tetrahydroquinoline 40A as well as two stereoisomers of the corresponding rearranged 7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinolines, 43A and 43B. The carbinols 39A and 39B prepared by the two different routes are therefore different.

As in the sulphur series, in all the above nitrogen heterocyclic syntheses stereochemical preferences were observed both in the rearranged as well as normal cyclodehydration products. The rearrangement products obtained by the cyclodehydration of the carbinols (38, 39B) can be rationalized by assuming the intermediary of N-arylazetidines such as 44.

Our preliminary attempts to prepare N-arylazetidines by the acid catalyzed cyclisation of 1-arylamino-3-alkanols (using sulphuric acid) gave only minor amounts of the N-arylazetidines and major reaction products were the normal and rearranged 1,2,3,4-tetrahydroquinolines.[11] Thus for the synthesis of N-arylazetidines, it was necessary to carry out the cyclodehydration reaction under basic conditions and also to convert the γ-hydroxyl group into a good leaving group. This was achieved by the treatment of the carbinol with triphenylphosphine dibromide in the presence of triethylamine whereby the carbinol group was presumably converted *in situ* to oxophosphinium bromide. The reaction mixture on work up gave a stereoisomeric

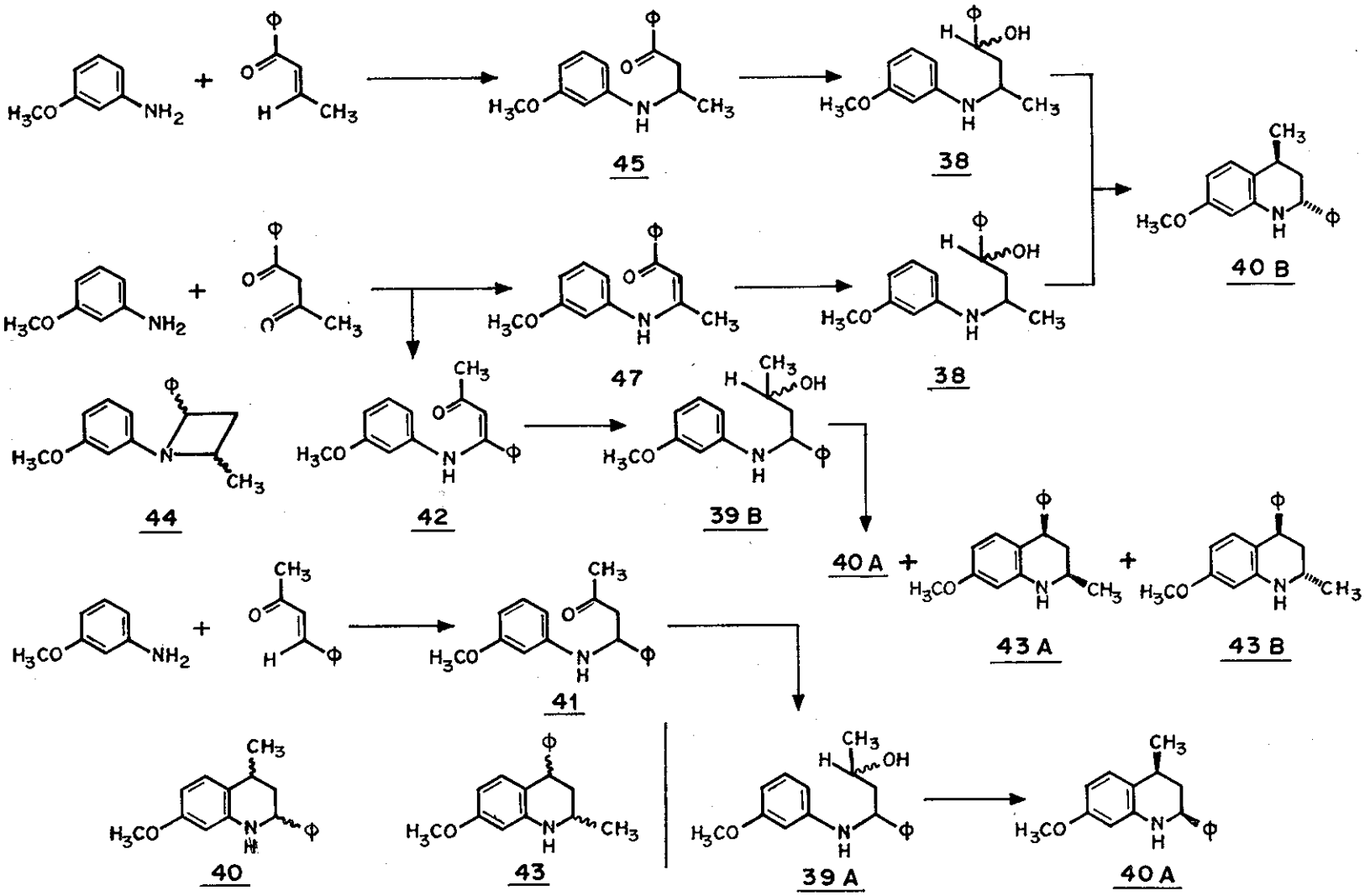


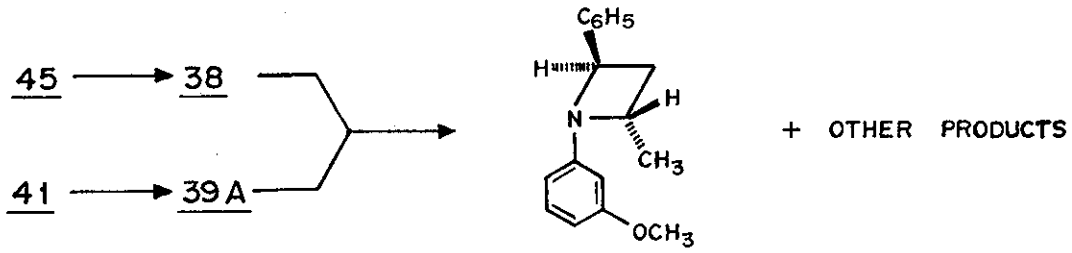
CHART - 9.

mixture of N-arylazetidines along with the corresponding mixed tetrahydroquinolines. A variation whereby the carbinol group was converted into the triphenylphosphonium-trichloromethyl derivative considerably reduced the reaction period.[12]

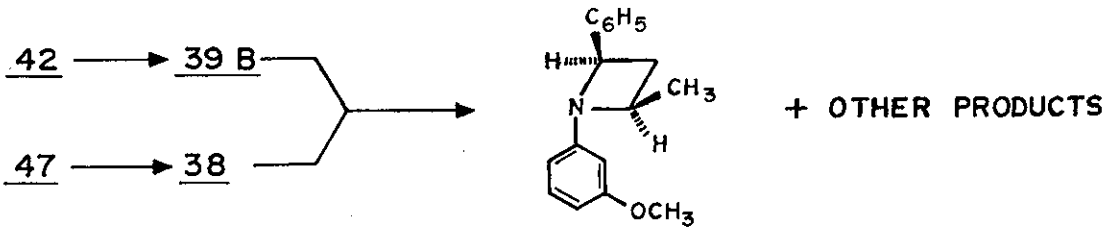
More stereoselective synthesis of N-arylazetidine was also achieved.[13] Thus carbinols 38 and 39A, prepared respectively by the reduction of the saturated ketones 45 and 41, on cyclodehydration under alkaline conditions as described above, gave essentially trans-2-methyl-4-phenyl-1-N-(3'-methoxyphenyl)azetidine 46B. On the other hand, carbinols 38 and 39B, prepared respectively by the reduction of the enamino-ketones 47 and 42, under identical conditions gave essentially the cis-2-methyl-4-phenyl-1-N-(3'-methoxyphenyl)azetidine 46A.

However this stereoselectivity was not evident in the case of N-arylazetidines arising from 3-(3'-methoxyphenyl)amino-2-methyl-1-phenylpropan-1-ol 48 and 4-(3'-methoxyphenyl)amino-3-phenylbutan-2-ol 49.[14] The latter were prepared by two alternate methods shown in Chart 11.

It was also observed by us that β-arylaminoethyl alkyl/cycloalkyl/aryl ketones[3,15] on cyclodehydration with fused zinc chloride and arylamine hydrochloride in

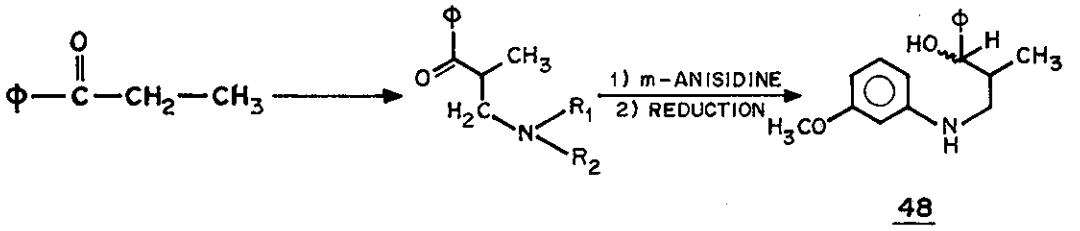


46 B



46 A

CHART - 10.



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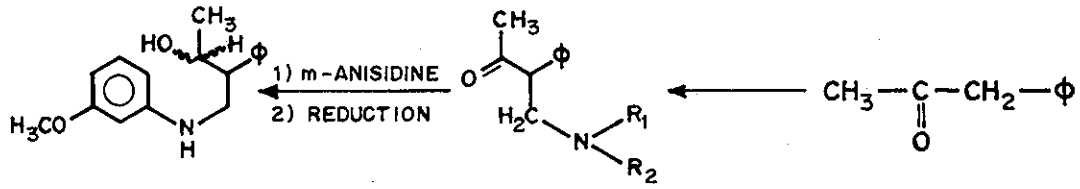

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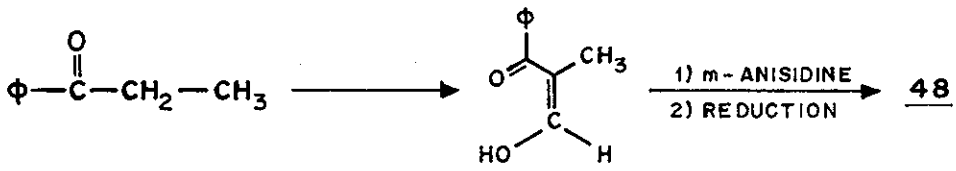


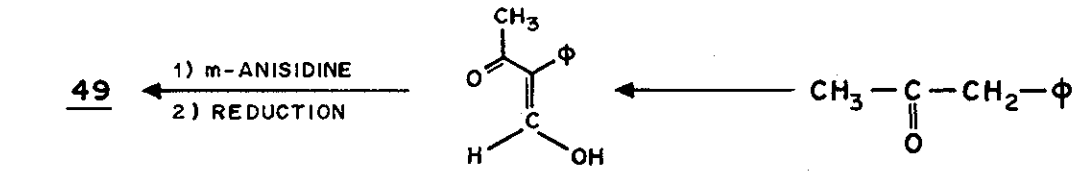


CHART – 11.

ethanol gave a mixture of rearranged quinolines and tetrahydroquinolines along with the normal cyclodehydration products (cf Chart 12). The formation of rearranged products is also explicable by envisaging the intermediate formation of N-arylazetidines 50 which have a leaving group as shown in Chart 12 or through the involvement of N-arylazetes 51 and 51A as shown in Chart 13.

Literature survey reveals that as against aziridines which have been widely studied, the chemistry of 4-membered saturated and unsaturated rings carrying one or more heteroatoms has not been much explored. We hope to continue our work in this area to get a better insight in their synthesis, stereochemistry and reactions. Thus our future objectives in this field are the synthesis of 1-S-phenyl-1-thioniumcyclobutane salts, N-arylazetine and N-arylazetes and a study of their structure, properties and reactivity.

This review article of authors' recent contributions is dedicated in humble tribute to Prof. R. B. Woodward with whom one of the authors (B. D. T.) had the privilege of spending a year (1960-1961).

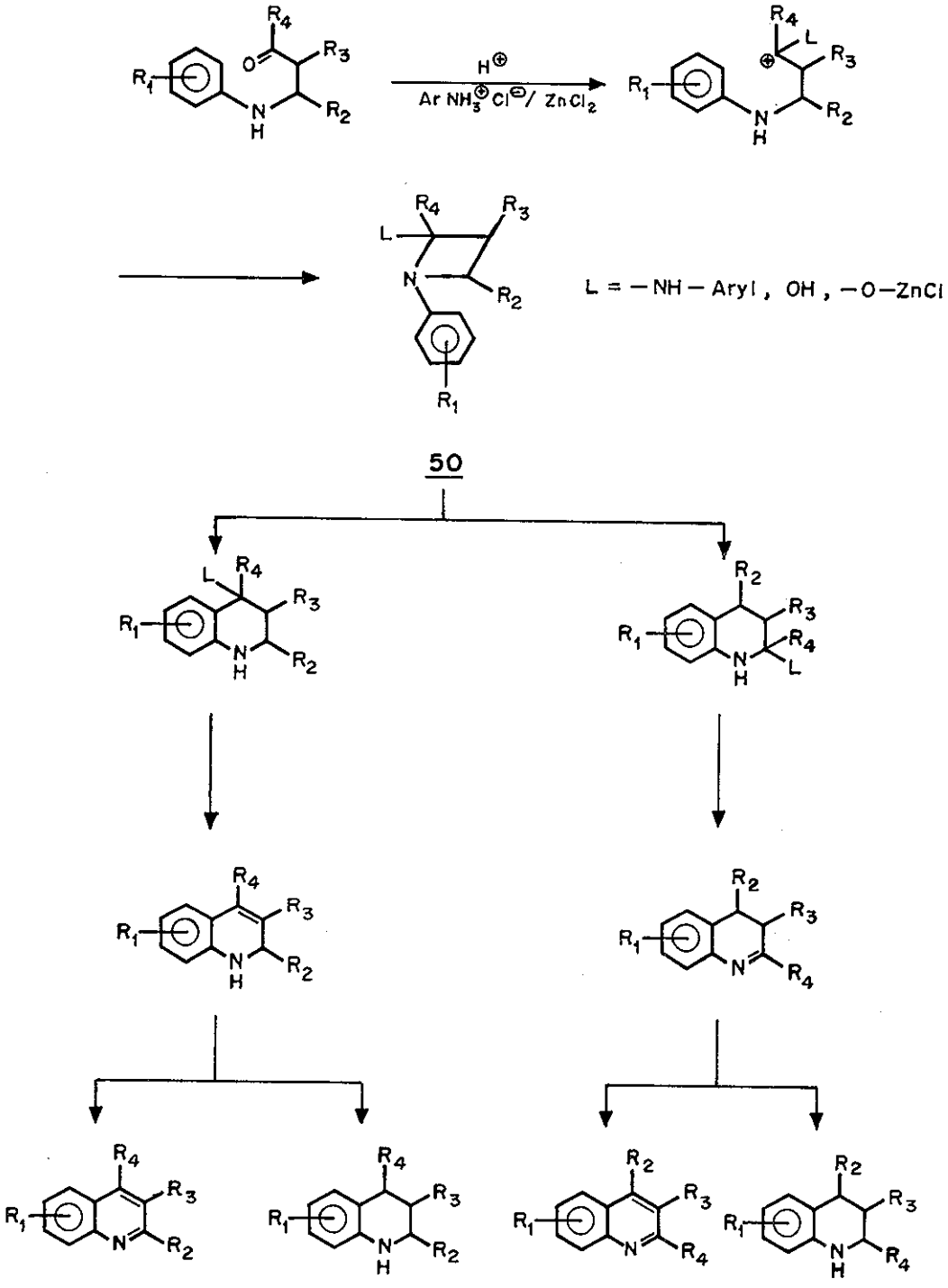
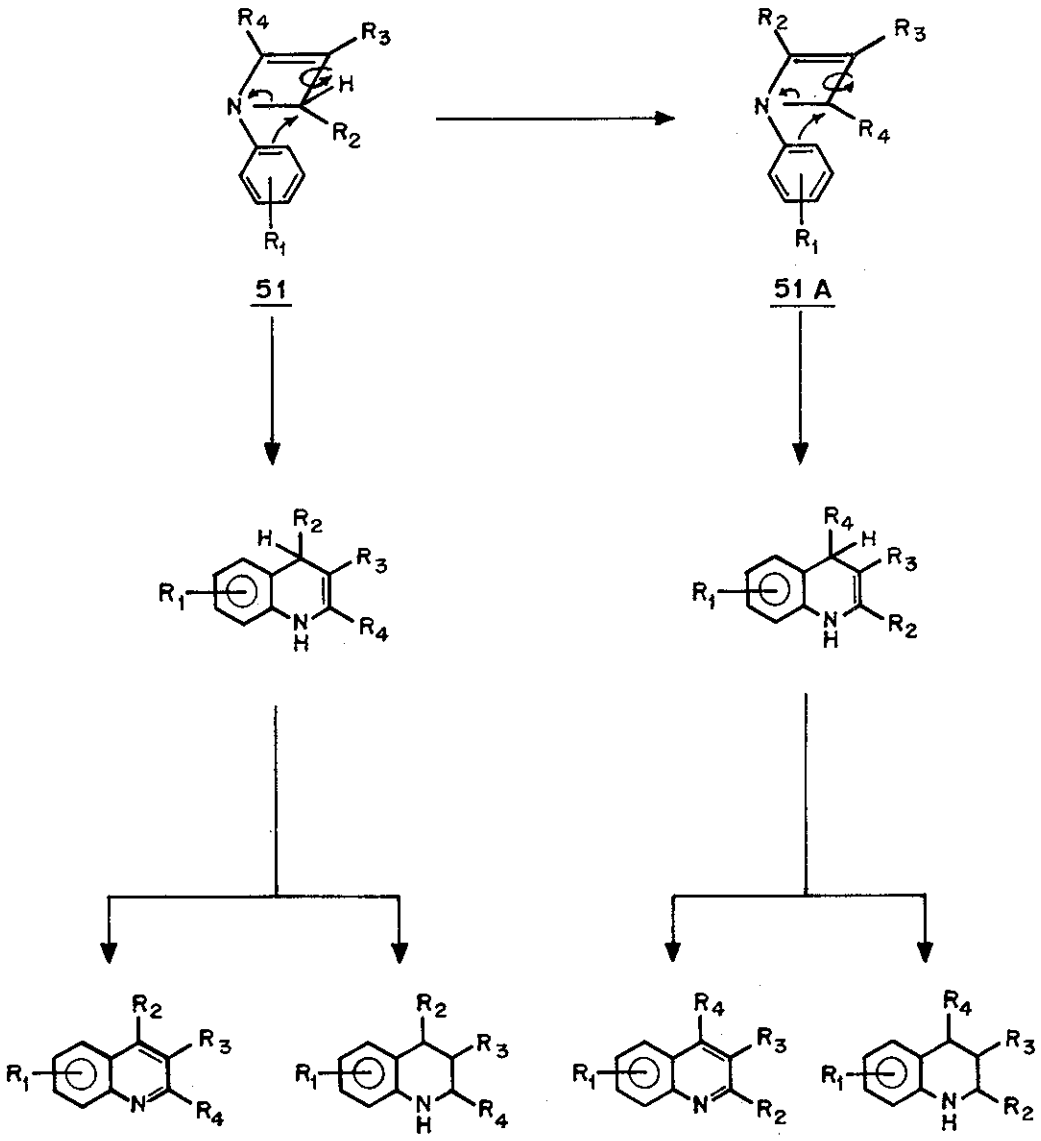


CHART -12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R3
H
N
R2
R1
51
R2
R3
N
R4
R1
51 A
R2
H
R3
R1
N
H
R4
R4
H
R3
R1
N
H
R2
R2
R3
R1
N
R4
R2
R3
R1
N
H
R4
R4
R3
R1
N
R2
R4
R3
R1
N
H
R2

CHART -13.

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