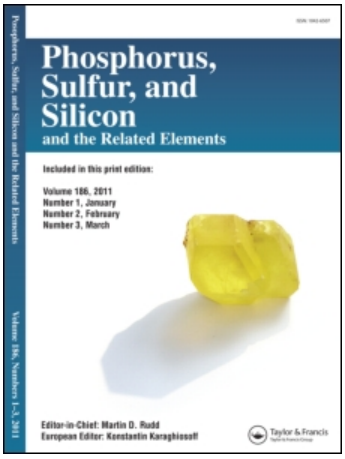

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TRANSFORMATION OF THIOPHENE DERIVATIVES INTO COMPOUNDS OF OTHER SERIES

L. I. BELEN'KII

Abstract Thiophene derivatives undergo some reductive transformations giving rise to numerous aliphatic, carbocyclic as well as to other heterocyclic systems. One type of these transformations includes as the first step the action of a reducing agent on thiophene compounds giving dihydro- or tetrahydrothiophene derivatives, and subsequent cleavage of the latter with another agent. While the use of catalytic hydrogenation in the thiophene series is essentially limited, there are now other methods - electrochemical reduction and ionic hydrogenation - leading to dihydro- and tetrahydrothiophenes, respectively. The other approach which is more widely used includes formally one-step reductive cleavage of thiophene rings with the scission of one or both C-S bonds. The most important methods of this type are reductive desulfurization with Raney nickel and the reductive cleavage by the action of alkali metals in liquid ammonia. In these processes thiophene plays the role of a "building block" the aromatic nature of which allows comparatively simple construction of a carbon skeleton bearing necessary substituents, the latter are retained or modified under the conditions of reductive cleavage; moreover during the cleavage new substituents may be originated creating exceptionally rich synthetic possibilities.

INTRODUCTION

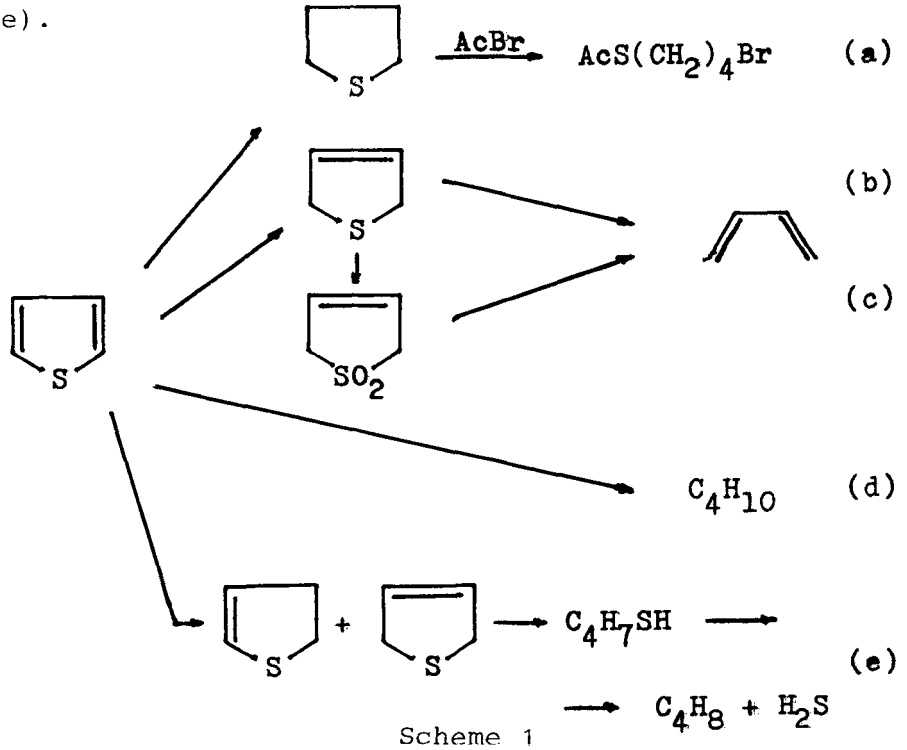
During 1oo years from its discovery by V. Meyer the chemistry of thiophene became one of the most developed parts of heterocyclic chemistry. Until the beginning of the 50's thiophene chemistry was developed mainly in well known analogy to benzene. However, in last years the reactions of thiophene having no analogy in benzene chemistry have assumed more importance. Just those reactions are of greatest interest which show the feature of thio-

phene as a heteroaromatic system with its own distinctive non-equivalence of the bonds in the ring, the specific geometry of the latter etc. To such processes various cleavage reactions of the thiophene ring belong leading to compounds of other series.

The aim of this survey is to consider the most important routes for the transformations of thiophenes into compounds of various types. More completely, those data will be presented which have been obtained in the Institute of Organic Chemistry of the USSR Academy of Sciences, particularly those of its laboratory of heterocyclic compounds headed by Prof. Ya.L.Gol'dfarb, where many pioneer investigations were performed in the field under discussion.

Some reductive processes are most useful for the transformations of thiophenes into aliphatic and carbocyclic compounds as well as into other heterocycles. There are two approaches to those transformations. One way includes as the first step the reduction of thiophene compounds to dihydro- or tetrahydrothiophenes which are interesting as such and can serve also as intermediates in the synthesis of various compounds belonging to other series. For example, there are some methods for the cleavage of tetrahydrothiophenes giving bifunctional aliphatic compounds [1,2]; diene systems having an open chain can be obtained by photolysis of dihydrothiophenes leading to the loss of sulfur [3] or by thermolysis of the respective sulfones proceeding with elimination of the SO_2 molecule (Scheme 1, a-c) [4,5]. The other approach which is more widely used includes formally an one-step cleavage of the thiophene ring resulting in the scission of one or both C-S bonds. The most important "one-step" methods are reductive desulfurization with Raney nik-

kel [6,7] and the cleavage with alkali metals in liquid ammonia [8-10]. It should be mentioned that these processes are really certain sequences of reactions; for example, at the beginning dihydrothiophenes can be formed which then undergo reductive cleavage (Scheme 1, d,e).



Scheme 1

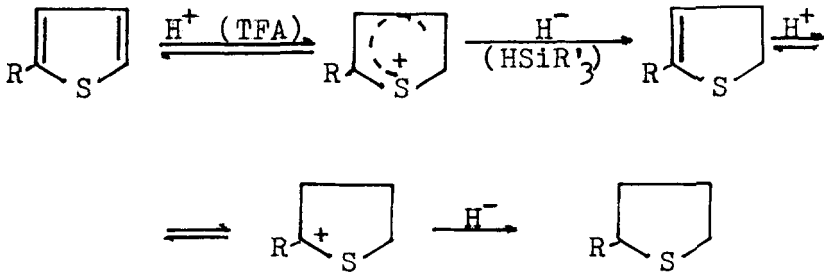
HYDROGENATION OF THIOPHENE TO DIHYDRO- AND TETRAHYDRO-THIOPHENE DERIVATIVES

The possibilities of catalytic hydrogenation of thiophenes are very restricted by the poisoning action of thiophenes on catalysts and also by the non-controlled ring destruction under hydrogenation conditions. Only few catalysts are suitable for hydrogenation of the thiophene ring, but their use is often limited by the high cost, drastic conditions, and low selectivity of the process. To some extent, palladium catalyst is an exception becau-

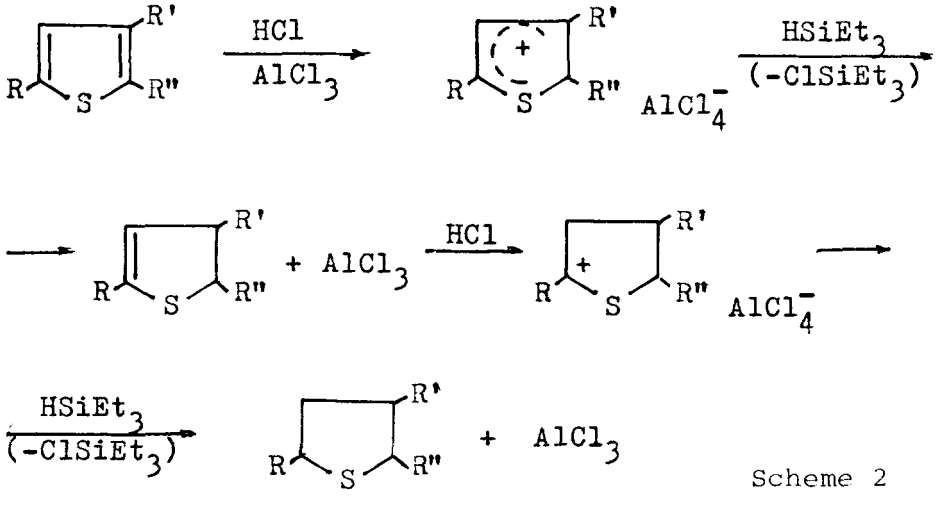
se it acts at moderate temperature and pressure [11]. But the poisoning action of thiophene compounds on this catalyst makes it necessary to use large amounts, almost equal to the quantity of the substances under hydrogenation. Therefore, the process is warranted only in special cases, for example, in stereospecific synthesis of biotin via the corresponding thiophenic precursor [12]. Tetrahydrothiophenes can be obtained in high yields using rhenium heptasulfide as catalyst [13,14], but drastic conditions (250-500°C, 100-300 atm) and the high price of the catalyst limit its use.

There are now quite convenient methods for the reduction of the thiophene nucleus that do not use heterogeneous catalysts; electrophilic ionic hydrogenation is one. It consists in consecutive reversible protonation and irreversible addition of hydride-ion and is carried out by means of trialkylsilane in proton acid medium (usually in trifluoroacetic acid). When applied to thiophenes the mechanism may be represented by Scheme 2 [15,16].

Various thiophenes bearing electron-releasing substituents enter into this reaction. Acylthiophenes under the conditions of ionic hydrogenation give alkylthiophenes which are then reduced to tetrahydrothiophenes. By ionic hydrogenation, alkyltetrahydrothiophenes with various terminal functional groups are obtained, for example with carboxy and dialkylamino groups. Mono- and diphenylthiophenes [17], 2,2'-bithiophene [18], benzo/b/thiophene and its homologues [19] also undergo ionic hydrogenation. tetradehydrobiotin is hydrogenated with difficulty and the yield of cis-biotin is only 10% [20], but the process is strongly facilitated in the case of some methylsubstituted tetradehydrobiotins [21].



R - Alk, Ar, R'CO, $(CH_2)_nNR'_2$, $(CH_2)_nCO_2H$



Scheme 2

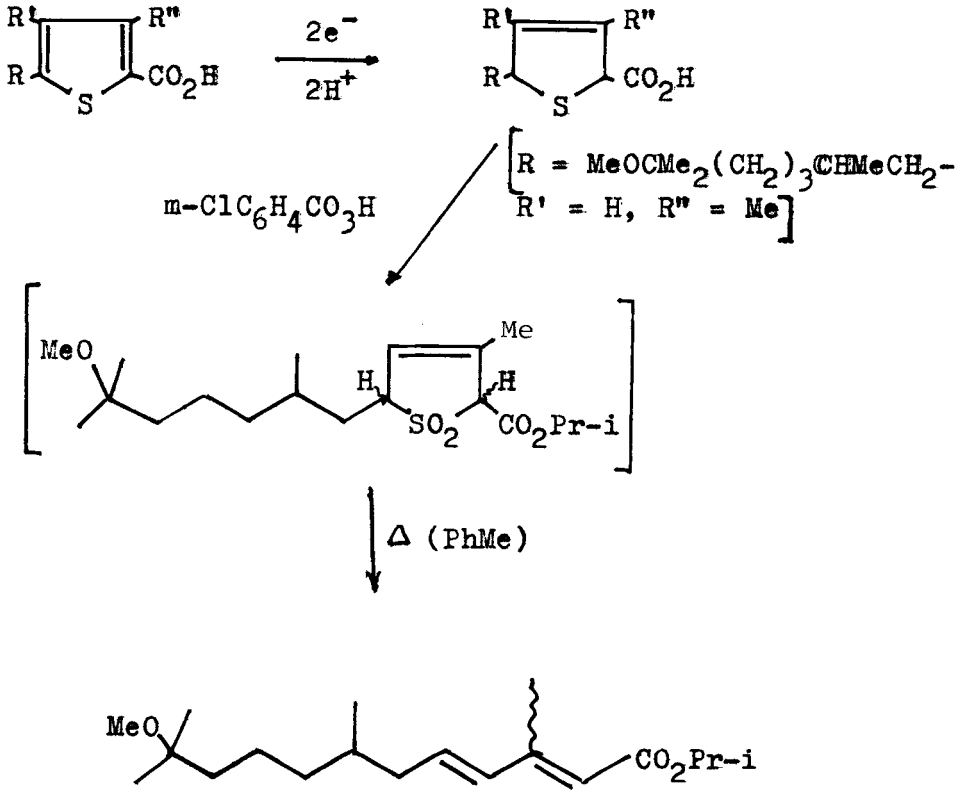
Under ordinary conditions (triethylsilane in CF_3CO_2H at 50°C) ionic hydrogenation of thiophenes proceeds very slowly (as a rule, it requires 20-60 h). The rate of the reaction is increased considerably by the presence of boron trifluoride etherate [22], p-toluenesulfonic acid, lithium tosylate, or lithium perchlorate [23]. With such additives (1-3% by weight) the hydrogenation of the thiophene ring proceeds at room temperature and is usually complete in 0.5-2 h. A study of the hydrogenation of stable σ-complexes [24] formed by protonation of alkylthiophenes led to the elaboration of the novel variant of thiophene ionic hydrogenation with the system tri-

ethylsilane - HCl - $AlCl_3$ (It should be noted that aluminium chloride can be used in catalytic amounts [25,26]). The use of the latter system not only accelerates the ionic hydrogenation as it takes place when the additives mentioned above are used, but also allows the hydrogenation of some compounds that are stable under the usual conditions of the reaction (triethylsilane in trifluoroacetic acid), for example, 2,5-diphenylthiophene.

Preparative electroreduction of thiophenes has now been developed considerably. It should be emphasized that direct reduction is practically unapplicable to thiophene and its homologues because of their high reduction potentials. The use of indirect reduction with the aid of electrochemically generated radical anions of other organic substances able to transfer an electron to a molecule, the reduction of which is very difficult, however, creates favorable possibilities, as shown by Mairanovskii et al. [27]. In particular, electrolysis of dimethylformamide solutions of thiophene in the presence of biphenyl as a "carrier" and 1o% water as a proton donor leads to the formation of dihydro- (53.8%) and tetrahydrothiophene (42.8%), the conversion being 55% [28].

Direct electrochemical reduction has been carried out successfully with thiophenecarboxylic acids that have an electron-withdrawing substituent stable under conditions of the process, and this substituent lowers considerably the reduction potential of the thiophene ring. It allows the easy transformation of 2-thiophenecarboxylic acid and its derivatives into the corresponding 2,5-dihydro derivatives, the yields being more than 9o% [29,3o]. The possibilities of the method were recently demonstrated in the synthesis of juvenoid methopren, the key step of which is the electrochemical reduction of a substituted

2-thiophenecarboxylic acid, subsequent steps being oxidation of the formed 2,5-dihydrothiophenecarboxylic acid and thermolysis of the sulfone obtained [31] (Scheme 3).



2E,4E/2Z,4E ~1:1

Scheme 3

REDUCTIVE DESULFURIZATION OF THIOPHENES WITH RANEY NICKEL

Reductive desulfurization under the action of Raney nikkel was discovered in 1939 by Bougault, Cattelain and Chabrier [6,7]. This reaction plays an exceptionally important role as a synthetic route making it possible to obtain compounds of various classes from thiophene derivatives and also as a method of structure elucidation of the latter. The synthetic importance of the reaction is determined by some distrinctive features. Owing to the

aromatic nature of the thiophene, various substituents can be introduced into its ring and these substituents are retained or changed in the process of reductive desulfurization. Sulfur elimination is followed as a rule by complete saturation of the four-carbon fragment of the thiophene ring. In the process of reductive desulfurization, elimination of sulfur from sulfur-containing substituents also takes place and, as a result, complete loss of substituents such as alkylthio-groups may occur. As substituents that do not contain sulfur and are transformed under the conditions of reductive desulfurization, one should mention the carbonyl group, which is reduced to the hydroxy-group. Fluorine atoms are retained under the reaction conditions, but in the case of other halogen derivatives, hydrogenolysis of C-X bonds takes place. Transformations of other substituents are observed more rarely. By conversion of thiophenes in the process of reductive desulfurization, various substances with straight or branched chains may be obtained, in particular, carbo- and heterocyclic compounds (if two atoms of the thiophene ring are linked by a chain). Thiophene can be used for lengthening aliphatic chains by four methylene units.

The mechanism of reductive desulfurization [32,33] probably includes the cleavage of C-S bonds with free radical formation (sulfur is bound in the form of nickel sulfide) and subsequent saturation of free valences and double bonds with hydrogen absorbed by Raney nickel. In some cases, for example, when the reaction is carried out in the presence of specially degassed or "aged" Raney nickel, the products of radical recombination are detected. However, under ordinary conditions (at 20-80°C in ethanol or methanol, with 5-10 times more Raney nickel in weight

than the thiophene compound and without any additional supply of hydrogen), desulfurization proceeds as a rule without difficulties and provides retention of the carbon skeleton. Complications may be associated with nonselective transformations of substituents.

Other skeletal metals are considerably less active than Raney nickel. A limited use in the syntheses of some aliphatic derivatives from thiophenes finds Raney cobalt[34,35] only. The skeletal reagent prepared from the aluminium - stainless steel alloy also appeared to be sufficiently effective (as compared with Raney nickel) [36]; but one should bear in mind that desulfurization conditions in the latter case were unusual and quite drastic (250-300°C with hydrogen addition at initial pressure 100-110 atm.).

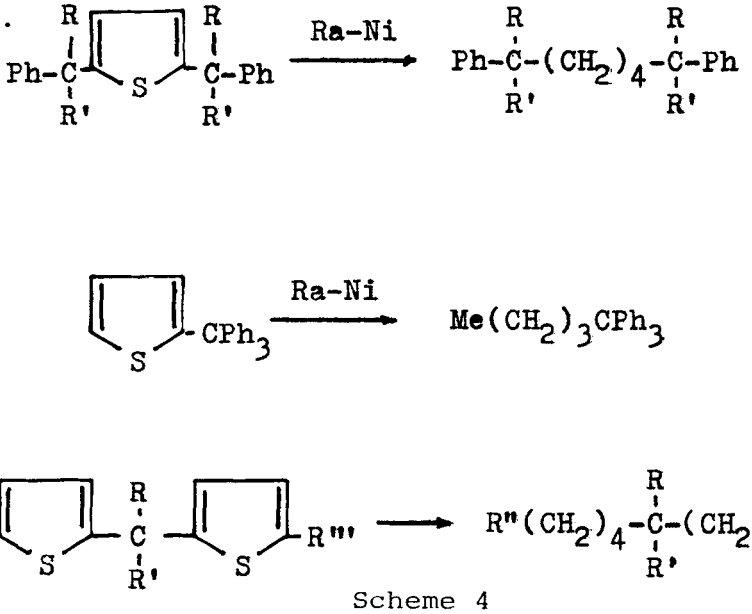
The number of published examples of reductive desulfurization of thiophene compounds exceeds at present 400. The available material is considered below, grouped according to related compounds formed as a result of reductive desulfurization. To avoid repetition, the substances of different classes are given as one group, if for the synthesis of starting compounds similar methods are used and the reaction proceeds along the same lines.

SYNTHESIS OF ALIPHATIC AND AROMATIC HYDROCARBONS, SOME F- AND Si-HYDROCARBONS

The preparation of aliphatic and aromatic hydrocarbons from thiophene derivatives proceeds similarly. Only in the case of some polycyclic systems a partial hydrogenation of benzene rings occurs [37,38]. Hydrocarbons can be obtained also by reductive desulfurization of chloro-, bromo- and iodo-substituted thiophenes; for example, 5-bromodibenzothiophene gives biphenyl [39]. Raney nickel does not affect the C-F bond; thus, reductive desulfuri-

zation of octafluorodibenzothiophene leads to octafluorobiphenyl in high yield [40]. Under reductive desulfurization conditions the C-Si bond is also retained, this makes it possible to prepare silanes [41].

Many authors have transformed thiophene derivatives into hydrocarbons with the object of elucidating the structure or studying the desulfurization conditions of various thiophenes. As purely preparative investigations several transformations should be mentioned: the syntheses of polyarylaliphatics[42,43], higher aliphatic hydrocarbons with straight chains [44,45] and tetraalkylmethanes [46,47] (Scheme 4).



Scheme 4

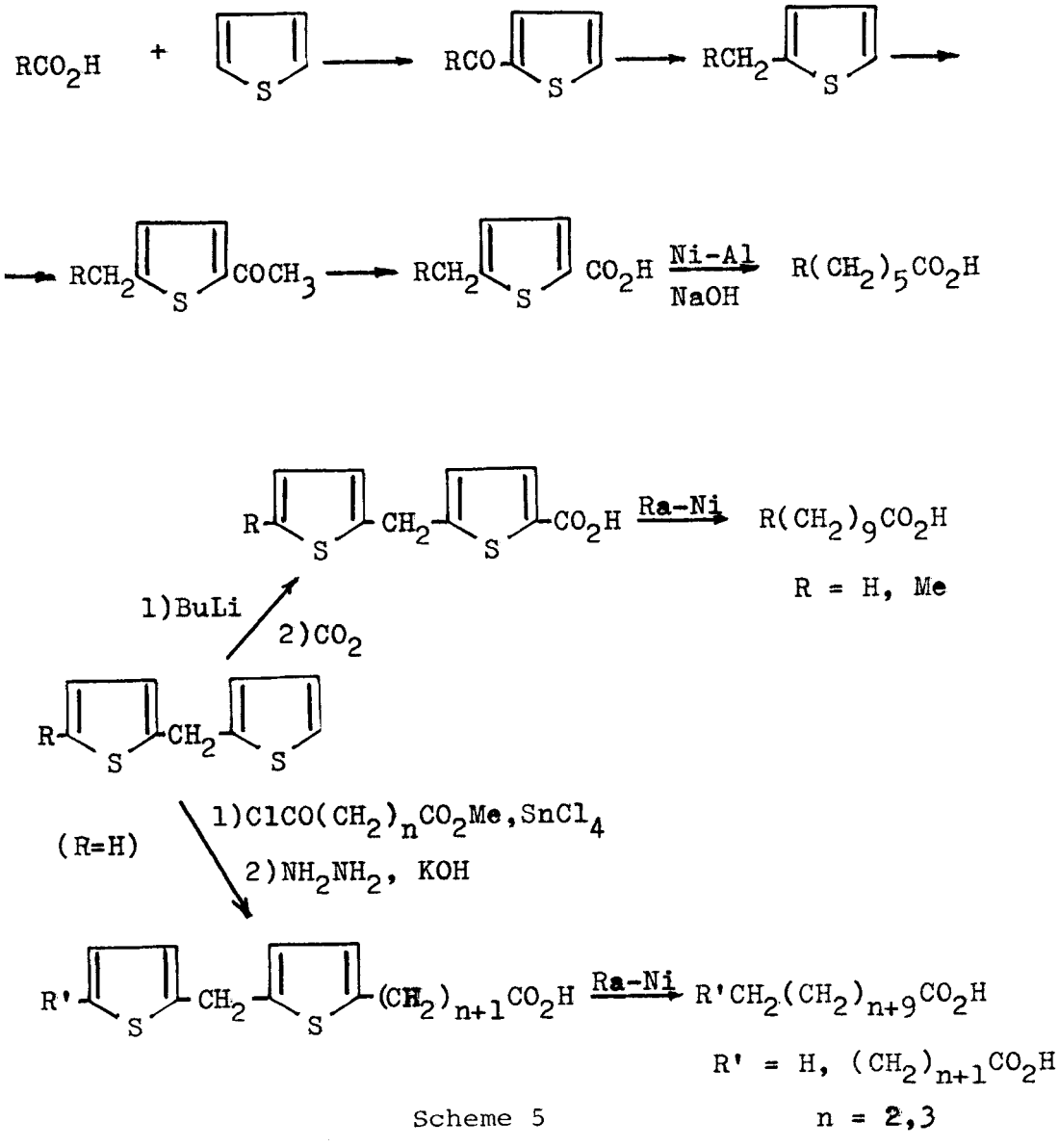
Reductive desulfurization helped to solve an important theoretical problem about the optical rotation value of compounds having four different alkyl groups at the asymmetric carbon atom. Wynberg et al. transformed optically active alkyl-substituted dithienylalkanes into hydrocarbons which proved to have very low optical rotation or were optically inactive [48,49].

SYNTHESIS OF CARBOXYLIC ACIDS

The first syntheses of aliphatic and arylaliphatic carboxylic acids using reductive desulfurization of some acids of the thiophene and benzo/b/thiophene series were described by Blicke and Sheets [50,51]. Results obtained by Papa, Schwenk and Ginsberg [52] were very important for the development of the synthesis of carboxylic acids from thiophenes. They demonstrated that desulfurization of acids may be carried out not only with Raney nickel, but also with an Ni-Al alloy in aqueous alkali. Later this very convenient modification of the reaction was often used by other investigators, it is termed the Papa-Schwenk method.

The synthetic potentialities of reductive desulfurization for the preparation of carboxylic acids were quickly appreciated by many authors. In 1954 a paper by Hansen [53] appeared which demonstrated that it was possible to obtain, by the use of thiophene, aliphatic acids with five carbon atoms more than the starting acid Scheme 5). Practically at the same time, many papers by Badger, Buu-Hoi, Gol'dfarb, Wynberg and their groups appeared in which the possibilities mentioned were widely used and applied to new classes of compounds.

The use of di(2-thienyl)methane is especially effective for the synthesis of long-chain mono- and dicarboxylic acids. It was studied in great detail by Buu-Hoi [54,55] and Gol'dfarb groups [56-59]. Acylation of the two free α-positions of di-(2-thienyl)methane with chlorides of dicarboxylic acid monoesters opened a short route to higher dicarboxylic acids with an odd number of carbon atoms [56,57]. The long-chain monocarboxylic acids can easily be obtained using monometallation or monoacylation of

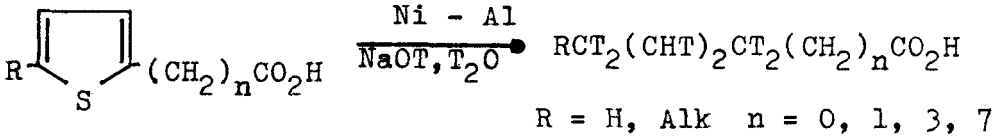


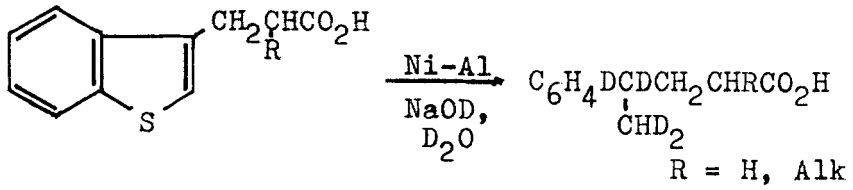
Scheme 5

di-(2-thienyl)methane [57-59] (Scheme 5).

Reductive desulfurization of optically active acids of the thiophene series was used for the elucidation of their configurations and the correlation of configurations of some aromatic and aliphatic compounds (Fredga[60], Petterson [61]).

Buu-Hoi et al. proposed an exceptionally simple method for obtaining aliphatic carboxylic acids labeled with deuterium or tritium, which consists in treating the carboxylic acids of the thiophene series with Ni-Al alloy in heavy or superheavy water in the presence of NaOD or NaOT [62-65]. Probably the only drawback of this method is that the hydrogen isotope is simultaneously introduced into several positions of the molecule, though these positions are easily determined by spectra [66].





X = Cl, Br

Scheme 6

The use of thiophene derivatives made it possible to introduce easily a ^{14}C label in a definite chain position and to obtain labeled higher aliphatic acids after reductive desulfurization [67].

SYNTHESIS OF KETONES, ALCOHOLS, ETHERS AND ACETALS

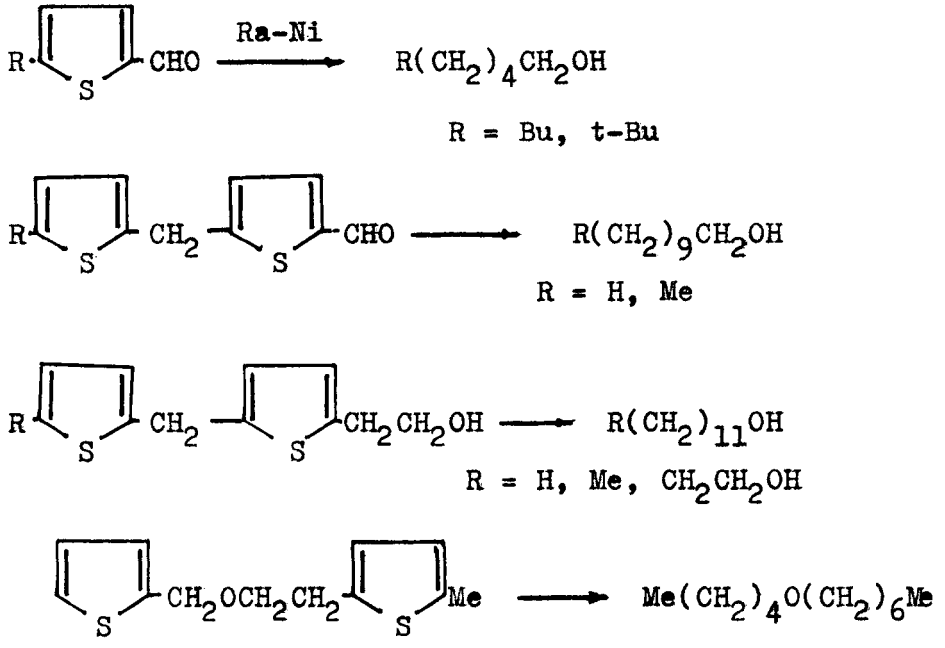
Reductive desulfurization of ketones of the thiophene series proceeds not so simple as in the case of carboxylic acids. In particular, in this process the transformation of the keto-group into a hydroxy group takes place to a certain extent [45,68,69]. Taking an insufficient amount of Raney nickel, one can avoid reduction of the keto group, but in this case the reaction does not proceed to the end and considerable amounts of diketones are formed which are the products of recombination of the intermediate radicals.

Gol'dfarb and Konstantinov showed that steric hindrance can promote the preservation of keto groups. Thus, they succeeded in obtaining butyl tert.-butyl ketone without any admixture of the corresponding alcohol from 2-pivaloylthiophene [69]. However, the attempts to desulfurize highly hindered ketones such as 3-acetyl-2,5-di-tert.-butylthiophene [68] and di-(2,5-di-tert.-butyl-3-thienyl)-ketone [69] were completely unsuccessful.

In some cases, the keto group can be retained if the reductive desulfurization is carried out in the presence of lower aliphatic ketones. This method was successfully used in the synthesis of macrocyclic ketones which will be considered below. It should be noted here that Stetter and Rajh when carrying out desulfurization in the presence of methyl ethyl ketone obtained several aliphatic and arylaliphatic diketones in 50-80% yields [70].

Reductive desulfurization of aldehydes of thiophene [68] and dithienylmethane series [44] is a very convenient method for the synthesis of primary alcohols the yields of which are up to 65%. Desulfurization of primary alcohols of the thiophene series leads to aliphatic alcohols without difficulties. As an example, the synthesis of higher al-

cohols from β-hydroxyethyl-substituted derivatives of dithienylmethane, described by Gol'dfarb and Kirmalova [58,59], (Scheme 7) can be given.



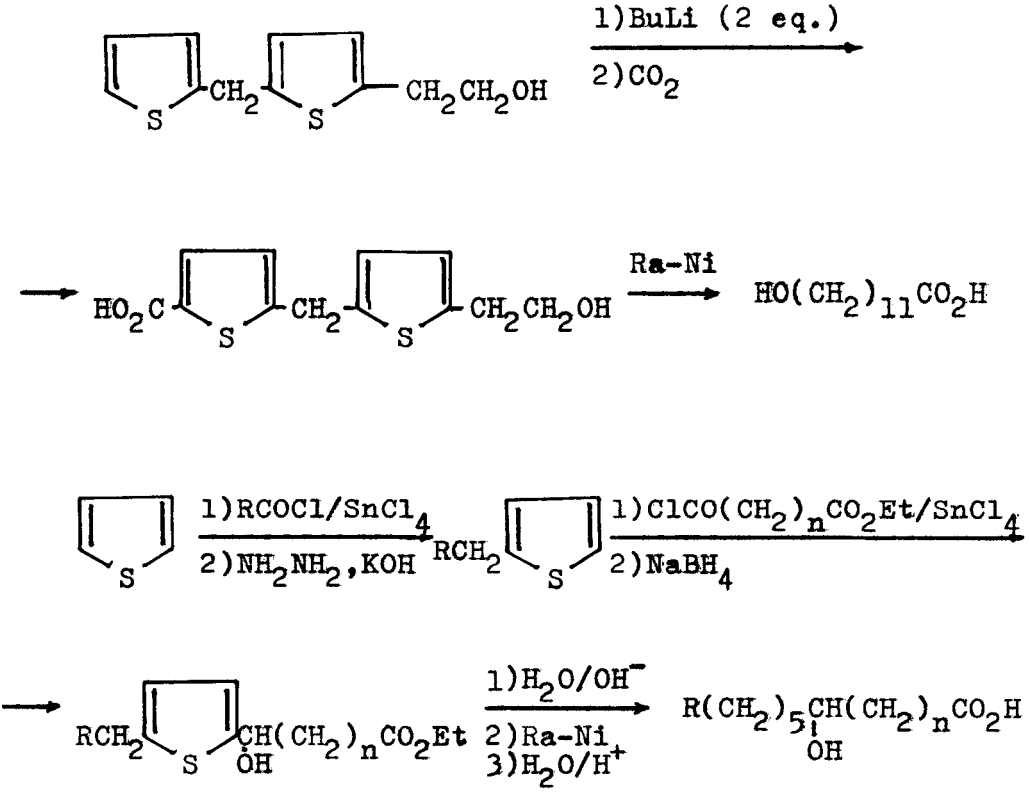
Scheme 7

The ether linkage does not change under the action of Raney nickel. Thus, Gol'dfarb and Konstantinov obtained some aliphatic ethers in yields of 5o-6o% (Scheme 7) [71]. Several arylaliphatic ethers were synthesized by different authors from the ethers of thiophene and benzo/b/ thiophene series.

Reductive desulfurization of the ethylene acetals of thiophene series leads, as Gol'dfarb and Konstantinov [69] showed, to the corresponding 2-alkyl-1,3-dioxolanes in yields of 4o-5o%; that is, transformation of an aldehyde into the cyclic acetal makes it possible to retain the aldehyde group under desulfurization conditions.

SYNTHESIS OF HYDROXY-, ALKOXY- AND KETOCARBOXYLIC ACIDS

The reductive desulfurization of hydroxy- and alkoxycarboxylic acids of thiophene series proceeds quite smoothly. Gol'dfarb and Kirmalova obtained the hydroxy acid as the result of the action of 2 eq. butyllithium on 5-(β-hydroxyethyl)-di-(2-thienyl)methane, followed by carboxylation. Desulfurization of this acid led to 12-hydroxydodecanoic acid in 94% yield [56] (Scheme 8). Miller, Haymaker and Gilman suggested another scheme for the synthesis of long-chain hydroxycarboxylic acids, which includes the preparation of 2-alkylthiophene, its transformation into a ketoester, reduction of the latter to the hydroxyester and desulfurization [72] (Scheme 8).

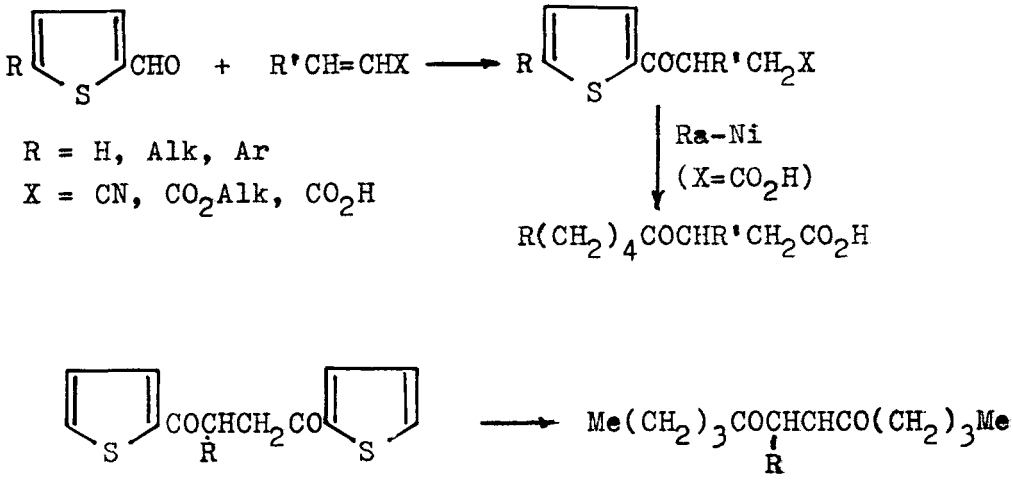


Scheme 8

Hydrogenolysis of optically active 2-thienylglycolic acid was used by Gronowitz for the correlation of the configuration of mandelic acid with that of hydroxy acids of the aliphatic series [73].

Reductive desulfurization of keto acids of the thiophene series can lead to aliphatic keto acids, hydroxy acids or their mixtures [74]. Keto groups directly bonded to a benzene ring can be reduced into CH_2 during hydrogenolysis [75].

Stetter and Rajh [70] proposed a new route to aliphatic and arylaliphatic keto acids that was already mentioned in connection with the synthesis of diketones. These authors obtained the thiophenic precursors in high yields using a novel and interesting procedure - addition of aldehydes of the thiophene series to α,β-unsaturated ketones, esters or nitriles in the presence of sodium cyanide. The keto esters and keto nitriles obtained in the last two cases are hydrolysed into keto acids which are subjected to reductive desulfurization as sodium salts in aqueous solution in the presence of methyl ethyl ketone (Scheme 9).



Scheme 9

SYNTHESIS OF ALIPHATIC AMINES

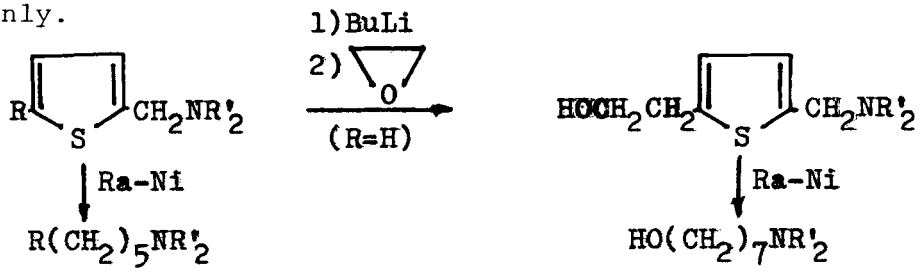
Reductive desulfurization of thiophene primary amines in ethanol is accompanied by the alkylation of the primary amino group hindering the isolation of the products. Such difficulties do not appear in the hydrogenolysis of tertiary amines of the thiophene series studied by Gol'dfarb and Ibragimova [76]. By introducing the β-hydroxyethyl group intc the thiophene ring of the tertiary amine mentioned, one can smoothly obtain the corresponding amino alcohols after hydrogenolysis [77] (Scheme 1o).

Gol'dfarb, Fabrichnyi and Rogovik obtained without difficulty the aliphatic diamines with tertiary and secondary amino groups from diamines of thiophene series. The possibility to obtain nonsymmetrical diamines is the peculiarity of this method [78]. Pastour and Barrat obtained symmetrical secondary diamines by reductive desulfurization of the Schiff bases that were formed from 2,5-thiophenedicarboxaldehyde and aromatic amines [79].

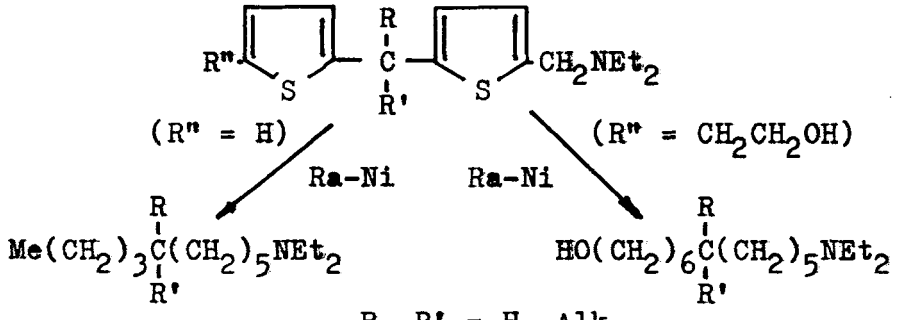
The possibilities of the synthesis of primary aliphatic amines from thiophenes have been studied by Gol'dfarb, Krasnyanskaya and Fabrichnyi. The undesirable alkylation under desulfurization conditions may be prevented by acylation of the thiophene amine or diamine [78,8o,81] (Scheme 1o). Červinka, Selovski and Koralova used desulfurization of the optically active amide for the determination of the absolute configuration of 1-(2-thienyl)ethylamine [82].

By carrying out the reductive desulfurization of thiophene ketoximes in the presence of ammonia it became possible to obtain also non-acylated primary amines [8o] (Scheme 1o). Under these conditions, aldoximes undergo Beckmann rearrangement. They were transformed into pri-

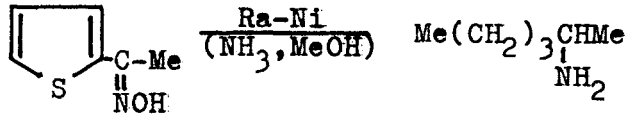
mary aliphatic amines by the use of Raney cobalt [80] only.

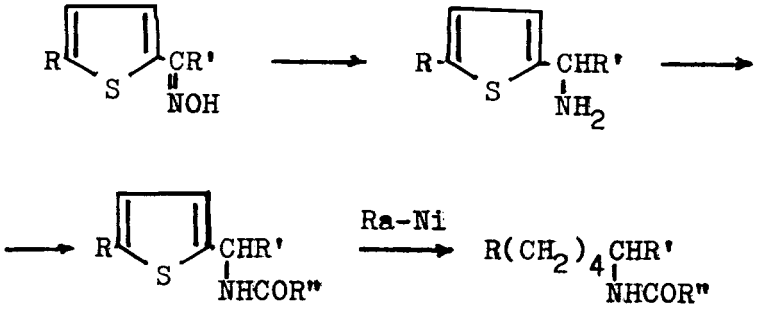


R = H, Alk, $CH_2NR'_2$
R' = Et or R'+R' = $(CH_2)_5$



R, R' = H, Alk





R, R' - H, Alk
R" - Me, Ph

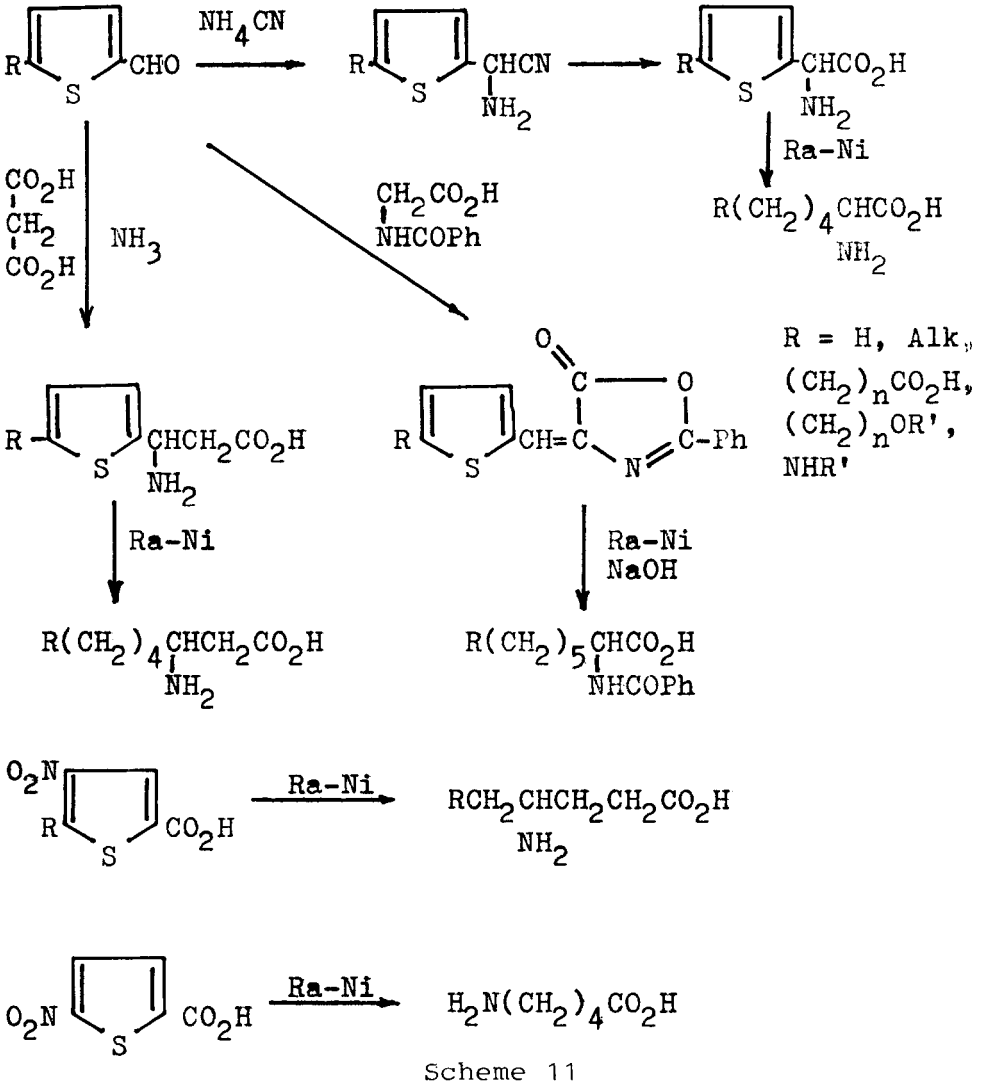
Scheme 1o

SYNTHESIS OF ALIPHATIC AMINO ACIDS

The routes to various aliphatic amino acids from thiophenes were elaborated mainly by Gol'dfarb, Fabrichnyi and Shalavina (see reviews [83,84]). Methods for the synthesis of amino acids with different mutual arrangement of amino and carboxy groups, in particular of α-,β-,γ-, δ-, ε -, ω-amino acids, of hydroxyamino acids, aminodicarboxylic and diaminomonocarboxylic acids were developed. Among these products there were obtained natural products and compounds not found in nature but of interest for the study of their physiological activity or for the synthesis of physiologically active substances. Though all synthesized amino acids have been obtained as racemates, it is in principle possible to obtain optically active substances using the resolution at the stage of the aliphatic or the thiophene acid. Many synthesized amino acids are of interest for the study of polycondensation processes. For the sake of brevity, synthetic methods considered below are classified according to the type of thiophenic precursor, but not to the type of the final aliphatic amino acid.

Thiophenecarboxaldehydes can be transformed into aliphatic α-amino acids with both straight and branched chains [85-89], α-aminodicarboxylic acids [89,90], diaminocarboxylic [89,91] and hydroxyamino acids [92] as well as into β-amino acids [93]. Nitrothiophenecarboxylic acids [84,94,95] or acylamino acids [95-97], which can be obtained easily from nitro acids, give by reductive desulfurization γ- and δ-amino acids (Scheme 11).

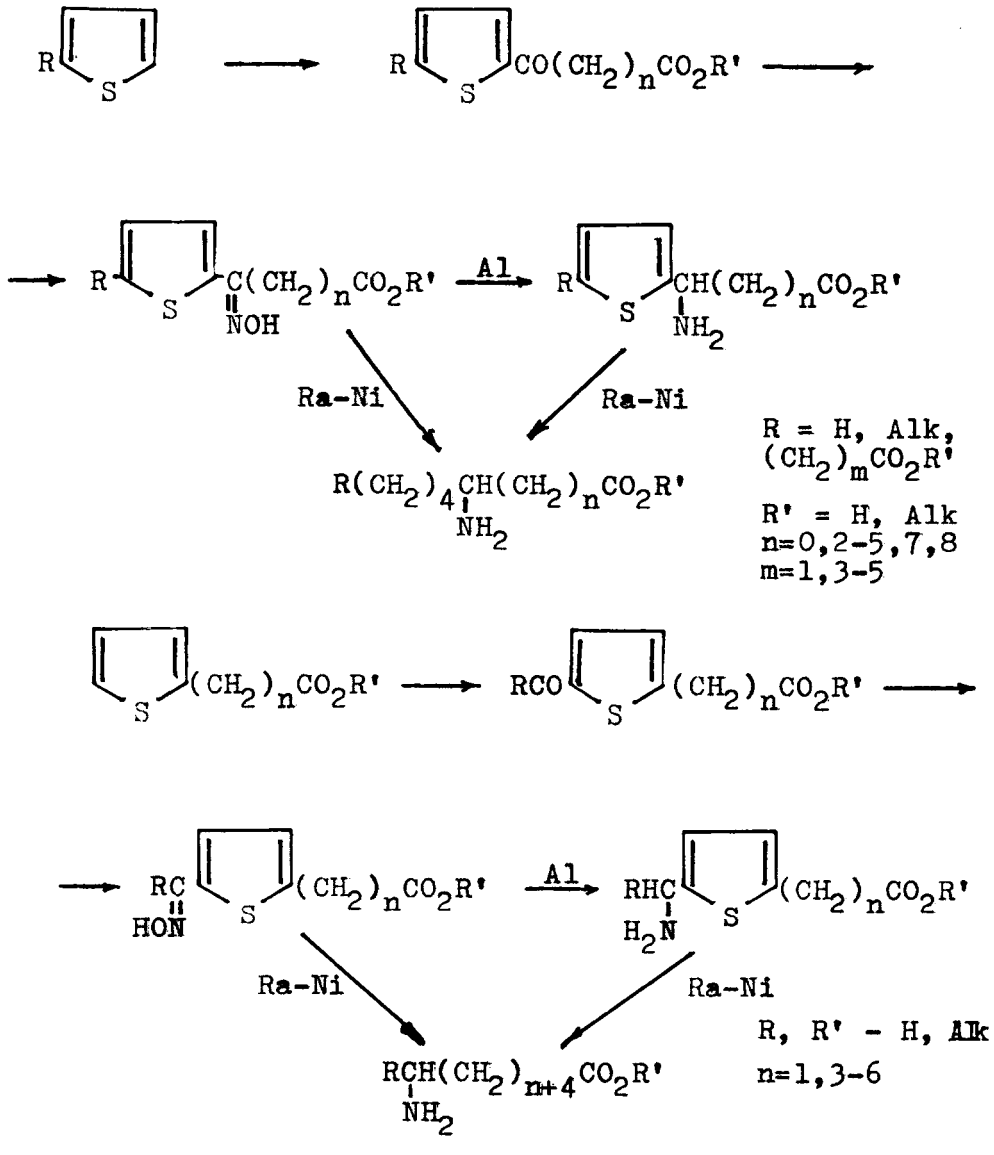
Owing to the accessibility of oximino acids and the possibility of their transformation into aliphatic amino acids, the methods based on the desulfurisation of oximino acids are the most universal syntheses of



Scheme 11

various amino acids. In many cases it is advisable to introduce an intermediate step, namely the reduction of the oximino acid into the amino acid of the thiophene series. Two variants of transformations of oximino acids wre elaborated [86,98-103] (Scheme 12). The first allows to obtain also aminodicarboxylic acids if esters of ω-(2-thienyl)alkanoic acids are used in the first step of the synthesis instead of thiophene homologues [90,103]. The

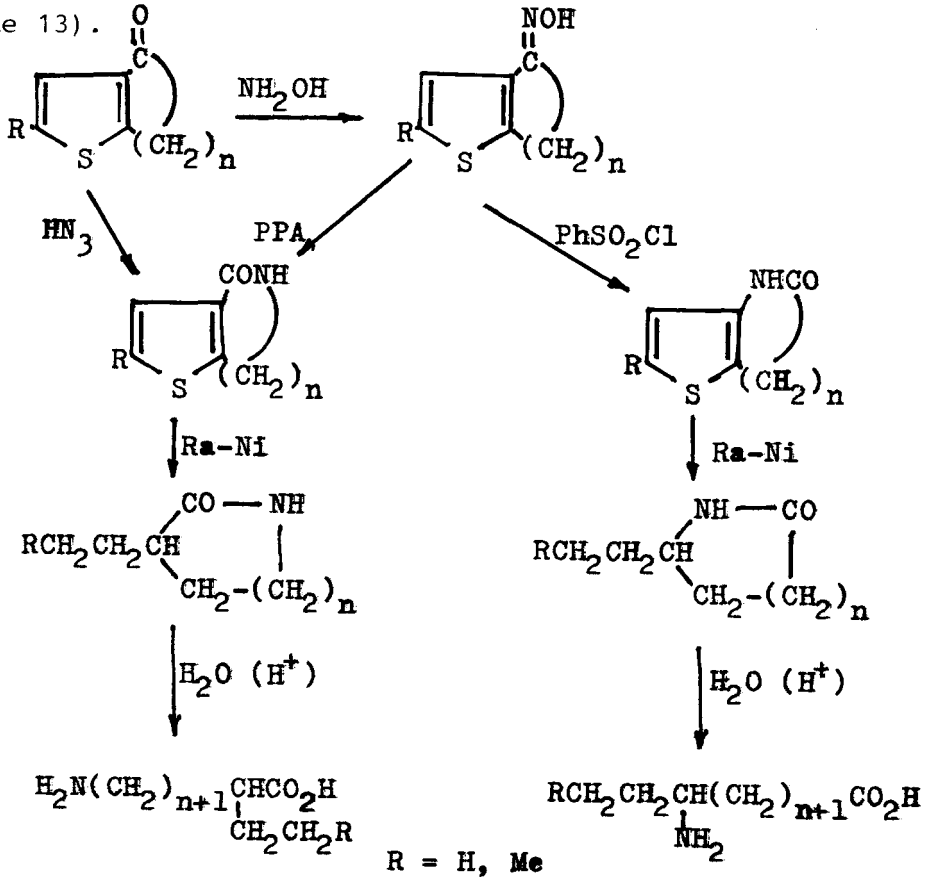
distinguishing feature of the second variant is that it makes possible the preparation of amino acids in which amino and carboxy groups are far from each other, in particular ω-amino acids [98,101,102].



Scheme 12

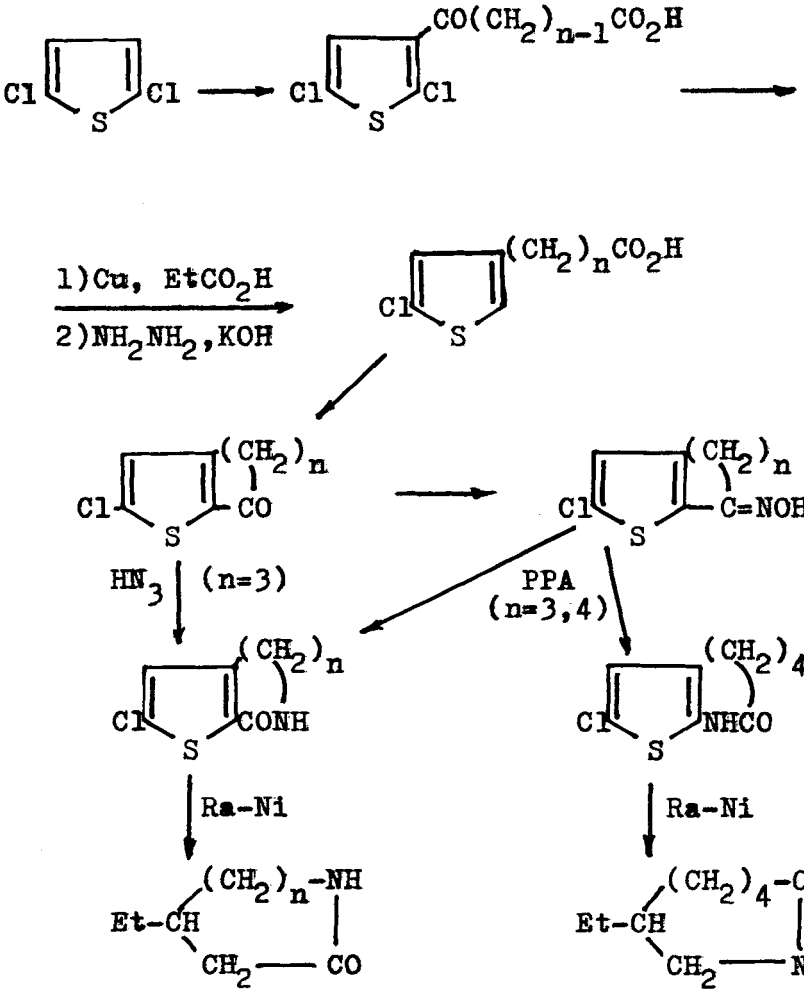
SYNTHESIS OF LACTAMS AND THEIR TRANSFORMATIONS

For the synthesis of substituted capro- amd oenantholactams Gol'dfarb et al. used reductive desulfurization of systems in which the lactam ring is fused with the thiophene ring (see [102,104-108]). In most of these syntheses the key intermediates are thiophene lactams of two types formed from the corresponding bicyclic ketones by Schmidt rearrangement or from their oximes by Beckman rearrangement. Reductive desulfurization of the lactams leads to ε- and ζ-alkylsubstituted ε-capro- and ζ-oenantholactams. By hydrolysis of these substances the corresponding ε- and ζ-amino acids were obtained. The action of Raney nickel on lactams of the second type leads smoothly to α-ethyl- and α-propyl-substituted lactams (Scheme 13).



Scheme 13

ζ -oenantholactam and ε -ethyl- ζ -oenantholactam [109] (Scheme 14). The synthesis of C-cyclohexyl- and C-cycloheptyl-substituted ε -caprolactams and ζ -oenantholactams was also described [110].



Scheme 14

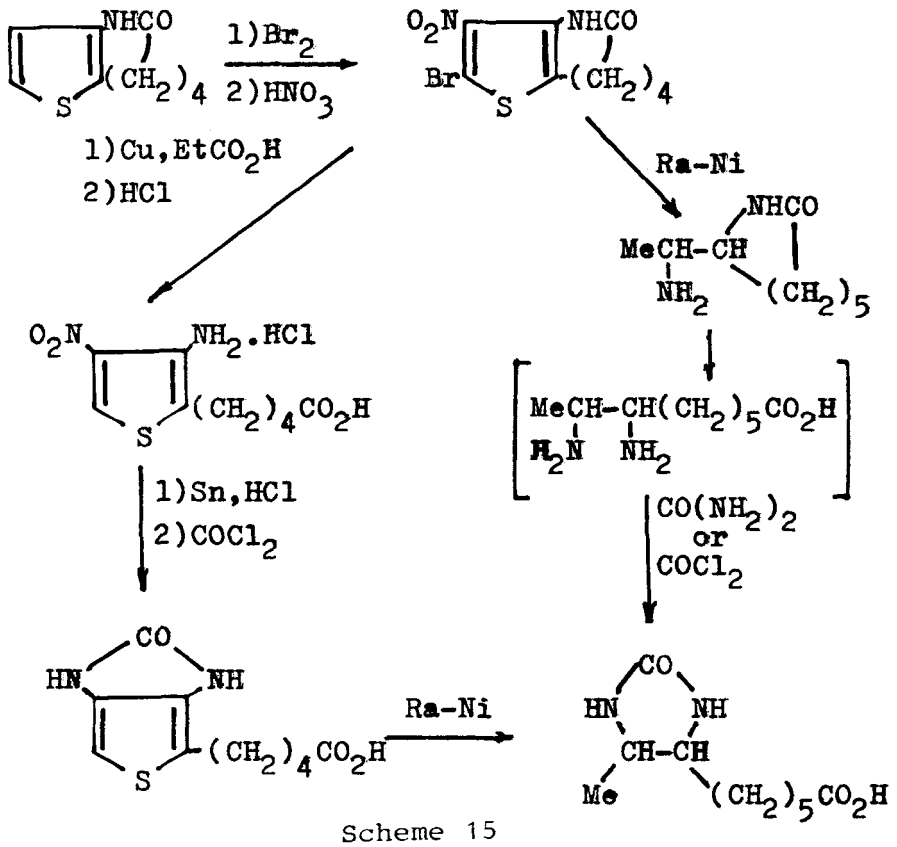
Lactams of the thiophene series proved to be useful intermediates in the synthesis of lactams of aliphatic aminodicarboxylic and diaminomonocarboxylic acids, which can then be transformed smoothly into the corresponding acids [111-113]. In the case of ε -(aminoalkyl)- ε -caprolactams and ζ -(aminoalkyl)- ζ -oenantholactams diaminocarboxylic acids are formed in which the amino groups are

separated by two- or three-carbon fragments. These structural peculiarities were used for the preparation of 2-oxoimidazolidine [113] and 2-oxohexahydropyrimidine [114] derivatives aided by the reaction of the above amino acids with urea. In a similar way (2-oxohexahydro-4-pyrimidinyl)alkanoic acids with a branched chain were also obtained.

The 2-oxoimidazolidine and 2-oxohexahydropyrimidine derivatives are of interest for the study of their biological activity. In particular, dethiobiotin and dethionorbiotin were among the synthesized substances which were obtained as mixtures of diastereoisomers. Dethiobiotin was also prepared with the help of reductive desulfurization of 2,3,4,5-tetradehydrobiotin[115], which in its turn was obtained from the lactam of δ-(3-amino-2-thienyl)-valeric acid [116] (Scheme 15). The obtained samples of dethiobiotin increased considerably the fodder yeast growth. A similar sample of dethiobiotin was also prepared directly from the lactam of δ-(5-bromo-4-nitro-3-amino-2-thienyl)valeric acid [115] (Scheme 15).

SYNTHESIS OF SOME CARBO- and HETEROCYCLIC COMPOUNDS

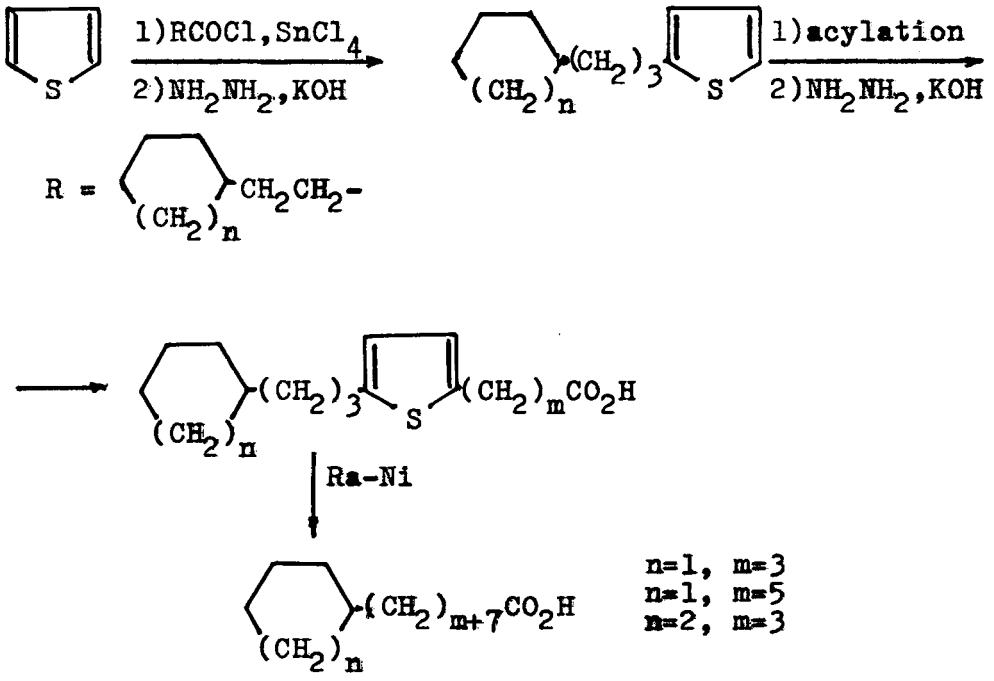
There are two approaches to the synthesis of alicyclic and heterocyclic compounds from thiophene derivatives. The first does not differ much from that used for the preparation of aliphatic and arylaliphatic compounds: the starting substances are alicyclic or heterocyclic derivatives and thiophene. This method is used both for lengthening the carbon chain and for incorporating substituents. The main features of such an approach were shown clearly in the paper by Buu-Hoi, Sy and Kuong [117] concerning the syntheses of dihydrohydnocarpic acid, dihydrochaulmoogric acid and also of an analogue for the former with a six-membered ring (Scheme 16). A synthetic



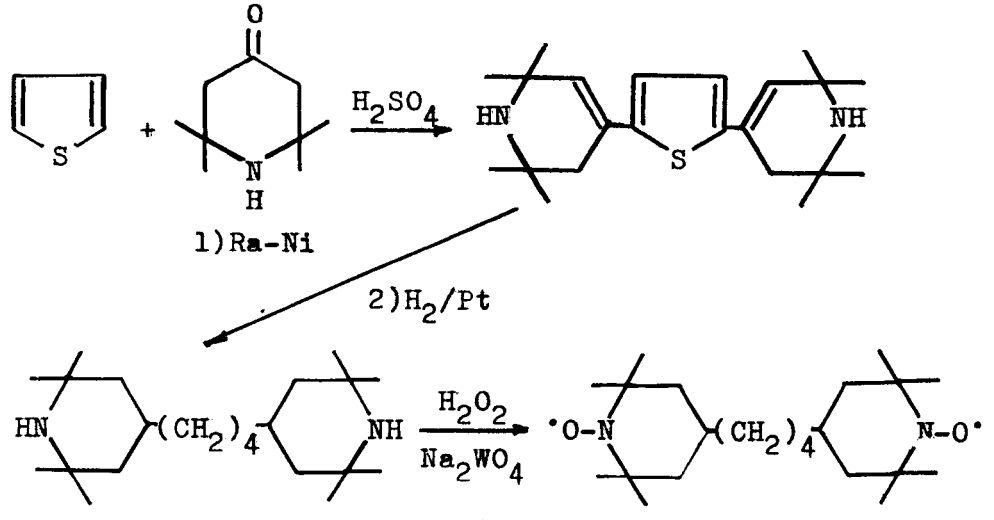
Scheme 15

route of the same kind was developed for the preparation of 1-alkyl-, 2-alkyl-adamantanes and also of ω-functionalized derivatives of the first of them by Hoeck, Strating and Winberg [118,119].

Gronowitz and Böler carried out reductive desulfurization of 5-(4-pyrimidyl)-2-thiophenecarboxylic acid into 5-(4-pyrimidyl)valeric acid [120] (Scheme 16). Myshkina, Stoyanovich and Gol'dfarb carried out hydrogenolysis of the sterically crowded diamines formed by azacycloalkenylation of thiophene with triacetoneamine and after additional hydrogenation obtained 1,4-(2,2,6,6-tetramethyl-4-piperidyl)butane which was used for the preparation of the stable iminoxyl radical [121] (Scheme 17).



Scheme 16



Scheme 17

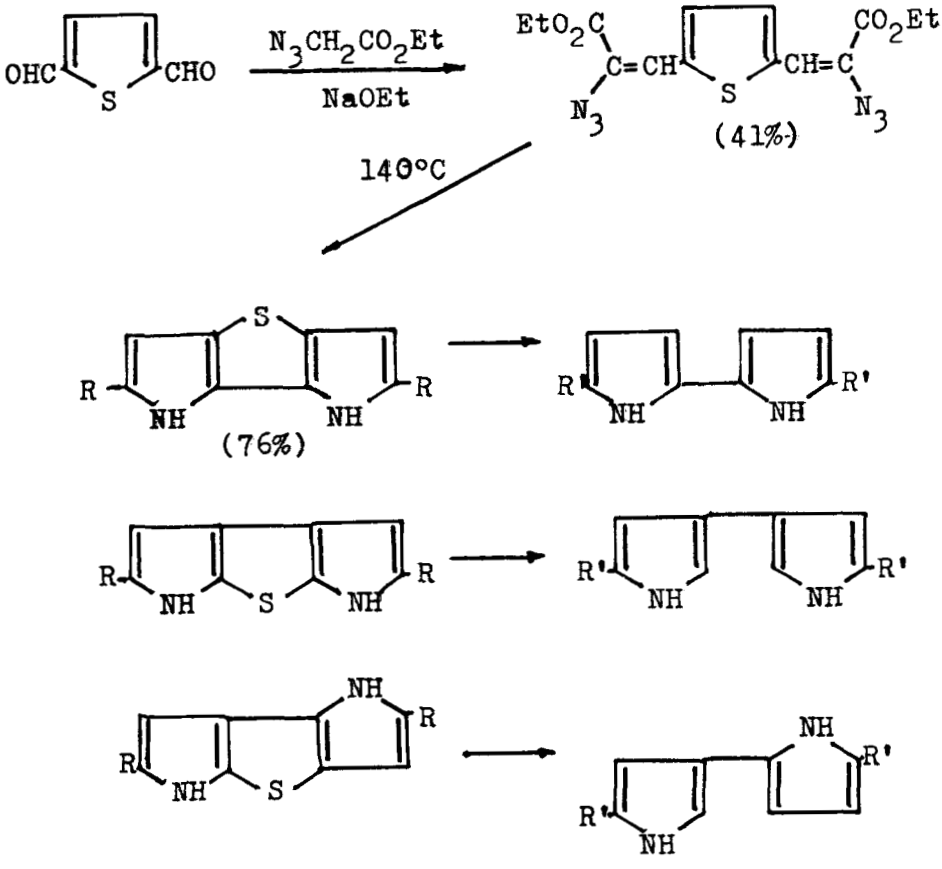
The characteristic feature of the second approach to the synthesis of cycloaliphatic and heterocyclic compounds is that carbon atoms of the thiophene ring are used to create the carbo- or heterocyclic skeleton itself. This approach has found adequate development in the new method of the synthesis of macrocyclic compounds which will be considered below. The same principle was used for the synthesis of substituted lactams from thiophene derivatives considered above as well as for the preparation of 4-phenylpyridine by desulfurization of benzothienopyridine (Kotake and Sakan [122]).

An interesting route to isomeric bipyrroles based on reductive desulfurization with subsequent hydrolysis and decarboxylation was proposed by Farnier, Soth and Fournari [123]. The yields at the desulfurization stage are in the range of 70-80% and this method may be regarded just as a synthetic method, since the same authors elaborated a sufficiently simple way to prepare thiophenic precursors in acceptable yields, starting with the corresponding thiophenecarboxaldehydes and azidoacetic ester [124] (Scheme 18).

There are interesting investigations devoted to the syntheses of six-membered heterocycles with boron and nitrogen as heteroatoms. The synthesis of borazarene derivatives, using reductive desulfurization, was described by Dewar and Marr [125]; Gronowitz et al. prepared a number of borazaropyridines [126, 127] (Scheme 19).

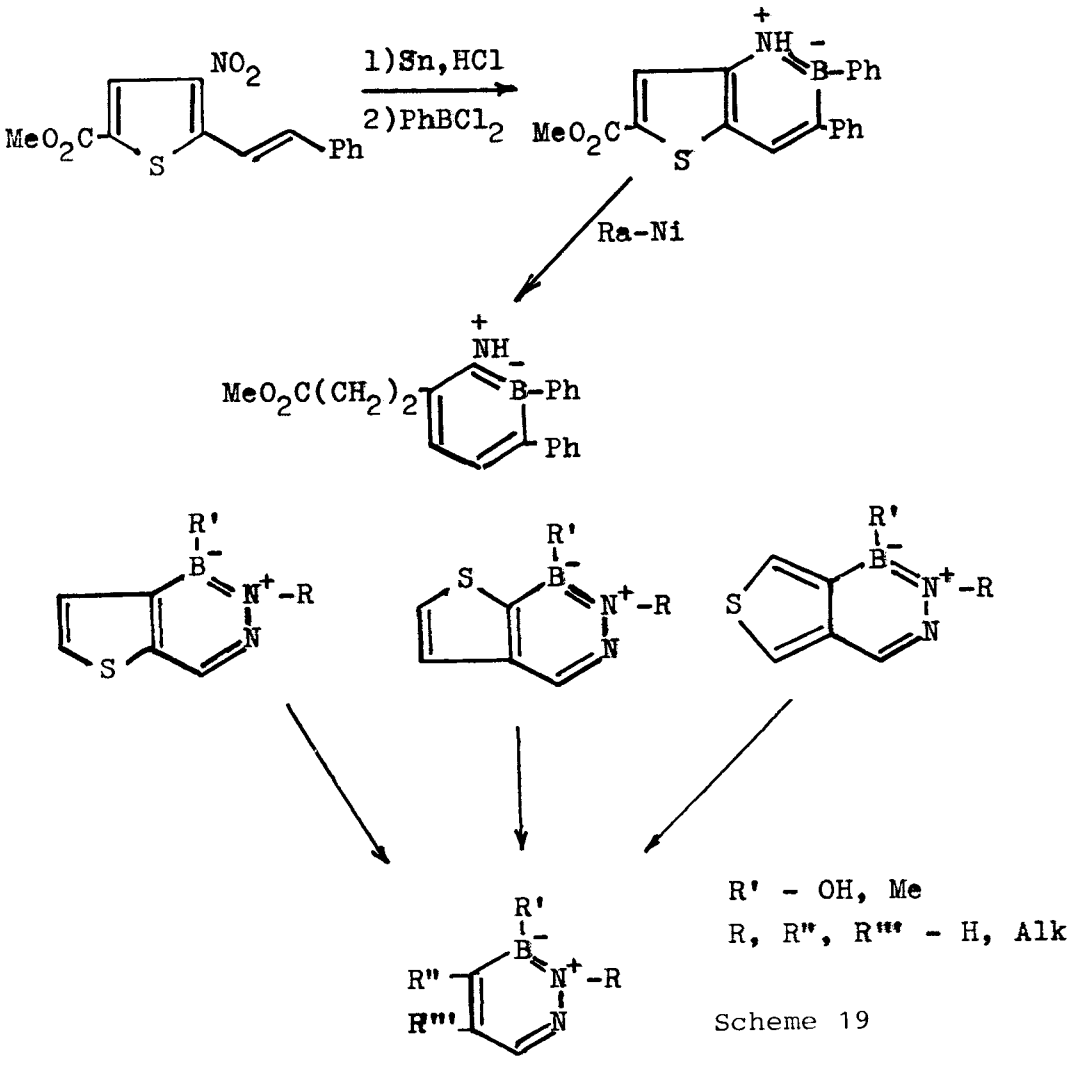
SYNTHESIS OF MANY-MEMBERED CARBO- and HETEROCYCLIC COMPOUNDS

For the synthesis of macrocyclic compounds with the aid of reductive desulfurization of thiophene derivatives,



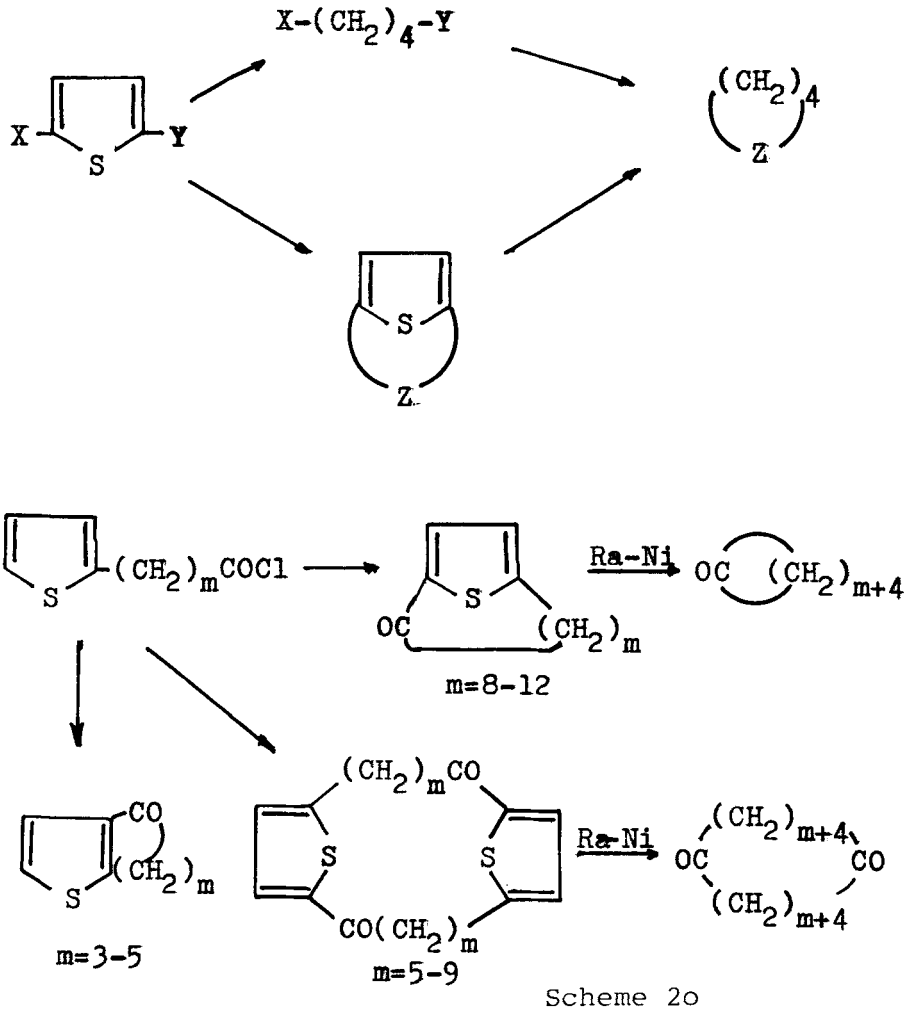
$R = CO_2Et$ Scheme 18 $R' = CO_2Et$, H

two principles may be used: 1) the preparation of long-chain bifunctional aliphatic compounds from thiophene derivatives and their subsequent cyclization by one of the usual methods; 2) the preparation of bi- or polycyclic compounds that possess the thiophene ring with the subsequent removal of the sulfur atom serving as a bridge (Scheme 2o). It is not necessary to discuss the first principle since the synthesis of long-chain bifunctional aliphatic compounds, for instance higher aliphatic dicarboxylic and hydroxy acids, using the reductive desulfurization of the corresponding thiophenic precursors has been elaborated by Buu-Hoi [54,55] and Gol'd-



Scheme 19

farb [56,57] groups, and these data were considered above. The second principle has a number of advantages when compared with the first. Cyclization may be facilitated by the presence of a "rigid group" (in this case, the thiophene ring) and give higher yields than using the first approach. Furthermore, the thiophene ring can be utilized not only for lengthening the carbon chain and incorporating substituents, it can also play the part of the second function, eliminating the necessity of incorporating the latter (see reviews [84,128,129]).



Scheme 2o

The principle given above for the synthesis of macrocyclic compounds was proposed in 1957 by Gol'dfarb, Taits and Belen'kii [13o]. Three routes to the precursors containing thiophene rings were elaborated. One method for the synthesis under consideration is the intramolecular acylation of ω-(2-thienyl)alkanoyl chlorides with subsequent conversion of the cyclization products by treatment with Raney nickel [13o,131] (Scheme 2o). This route is especially attractive because it does not require the

preparation of a bifunctional thiophene compound (the role of the second function is played by the unsubstituted α-position of the thiophene ring) and this makes it easier to prepare the starting compounds. In other words, with this method one can make full use of the advantages of the thiophene-based synthesis of macrocycles.

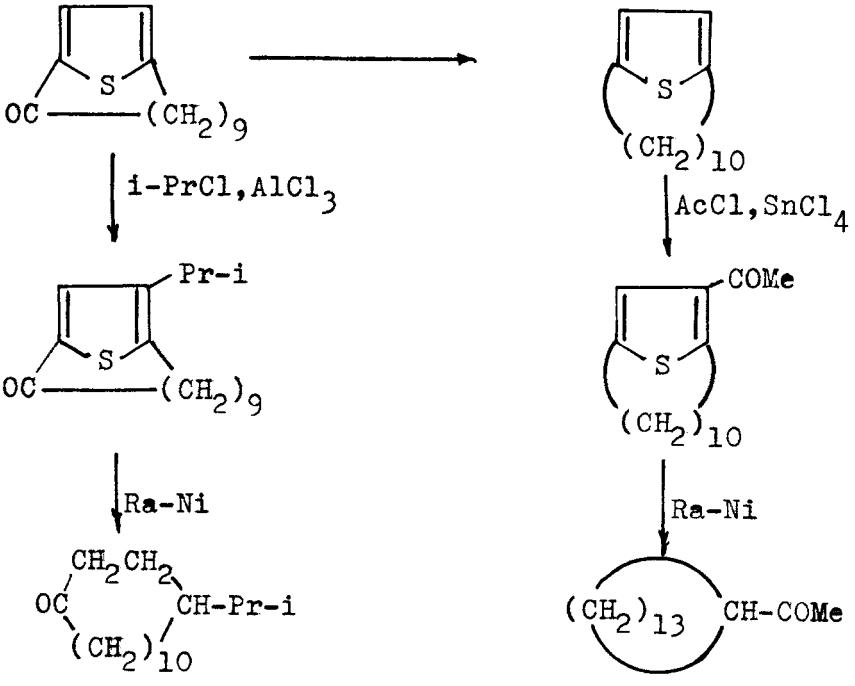
For the preparation of the higher ω-(2-Thienyl)-alkanoic acids a novel and convenient method was elaborated using as intermediates ω-chloroalkyl-2-thienylketones and starting with the accessible ω-chloroalkanoic acids [132]. Various conditions of the cyclization of ω-(2-thienyl)-alkanoyl chlorides have been studied [128,13o,133-135]. In particular, it was found that the presence of an inert solvent, as well as an increasing concentration of the condensing agent in a homogeneous medium, leads to higher yields of bicyclic ketones possessing the thiophene ring [135].

It was found that by addition of acetone to the solvent mixture, the macrocyclic ketones are desulfurized without affecting the carbonyl group, and the yields of a number of cycloaliphatic ketones amounted to 7o-9o%. Among them were macrocyclic ketones with a musk odor, such as cyclotetradecanone, exaltone, cyclohexadecanone and dihydrocivetone [13o,131] (Scheme 2o).

One can reduce the keto group in the cyclization products and introduce substituents into the thiophene ring which are retained after desulfurization. γ-Isopropylcyclotetradecanone and acetylcyclotetradecane were obtained by this route [136] (Scheme 21).

Bicyclic ketones with thiophene rings bearing a methyl group were obtained starting with 2- and 3-methylthiophenes [137-139]. On reductive desulfurization of the ketones obtained from 2-methylthiophene α-ethyl- and α-propylcycloalkanones were obtained (Scheme 22). In the

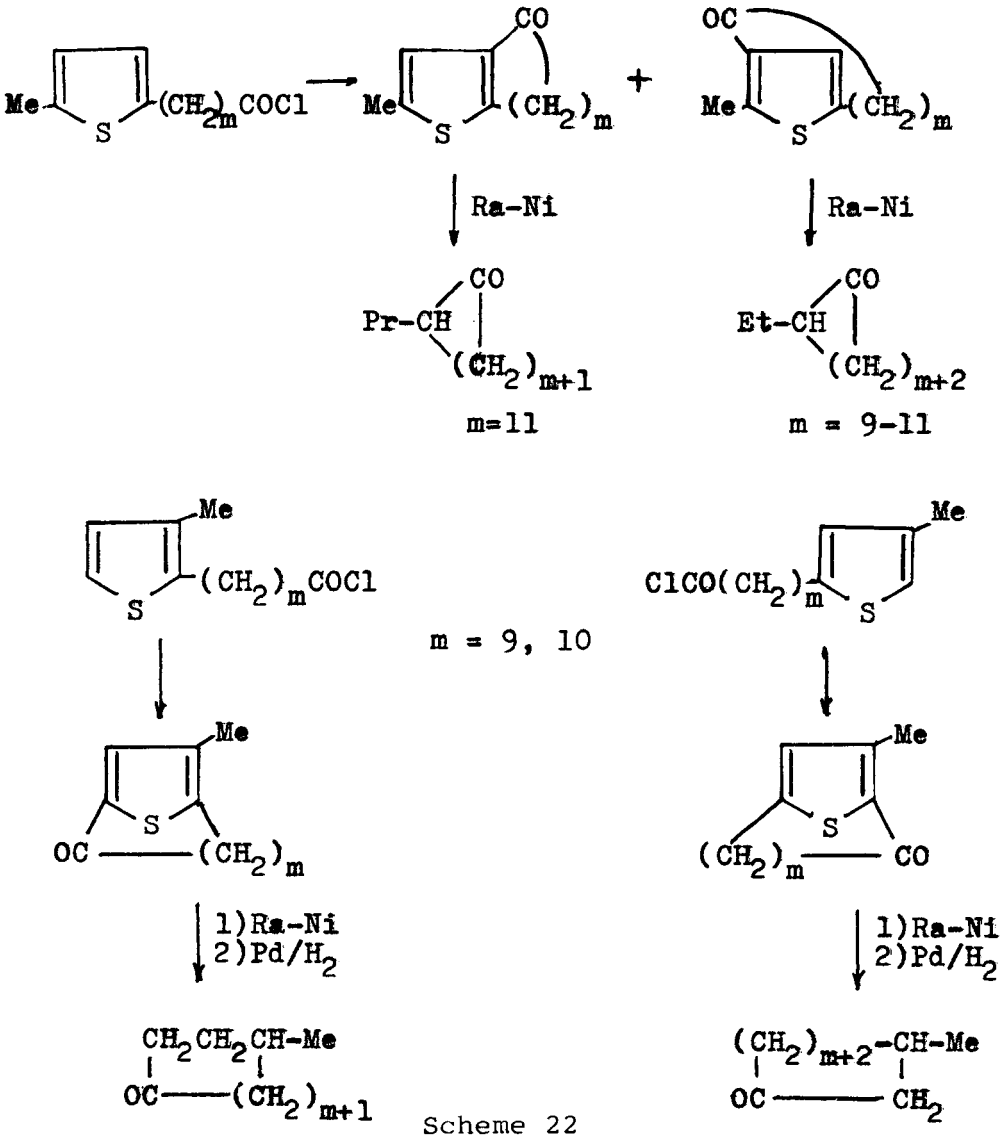
case of 3-methylthiophene, mixtures of the products of acylation in positions 2 and 5 in the ratio ~ 2:1 are formed: these products can be separated using chromato-



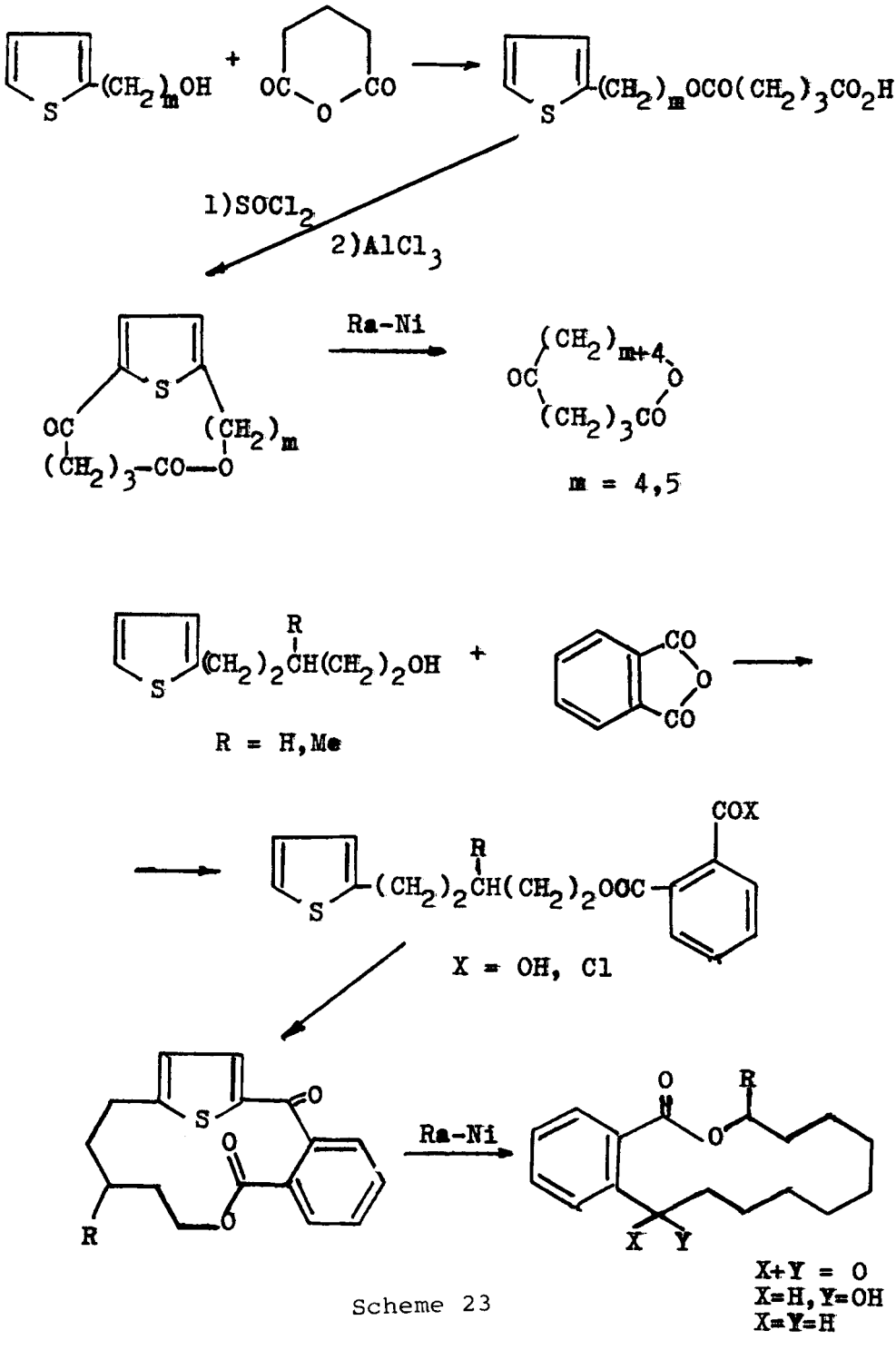
Scheme 21

graphy on alumina. Subsequent transformations of these keto acids into carboxylic acids, then into chlorides and finally intramolecular acylation of the latter leads to bicyclic ketones. The sulfur removal by reductive desulfurization of these ketones in an ethanol - acetone mixture proceeds sufficiently rapidly, but in the reaction products unconjugated C=C bonds were retained, which demands additional hydrogenation over palladium-charcoal. As the result β- and γ-methylcycloalkanones including racemic β-methylcyclopentadecanone (muscone) are obtained (Scheme 22).

A similar method may also be used for the preparation of many-membered heterocycles with heteroatoms other than sulfur. Taits, Alashev and Gol'dfarb [14o] described the synthesis of macrocyclic ketolactones including intramolecular acylation of ω-(2-thienyl)alkyl alkanedicarboxylate chlorides and reductive desulfurization



Scheme 22

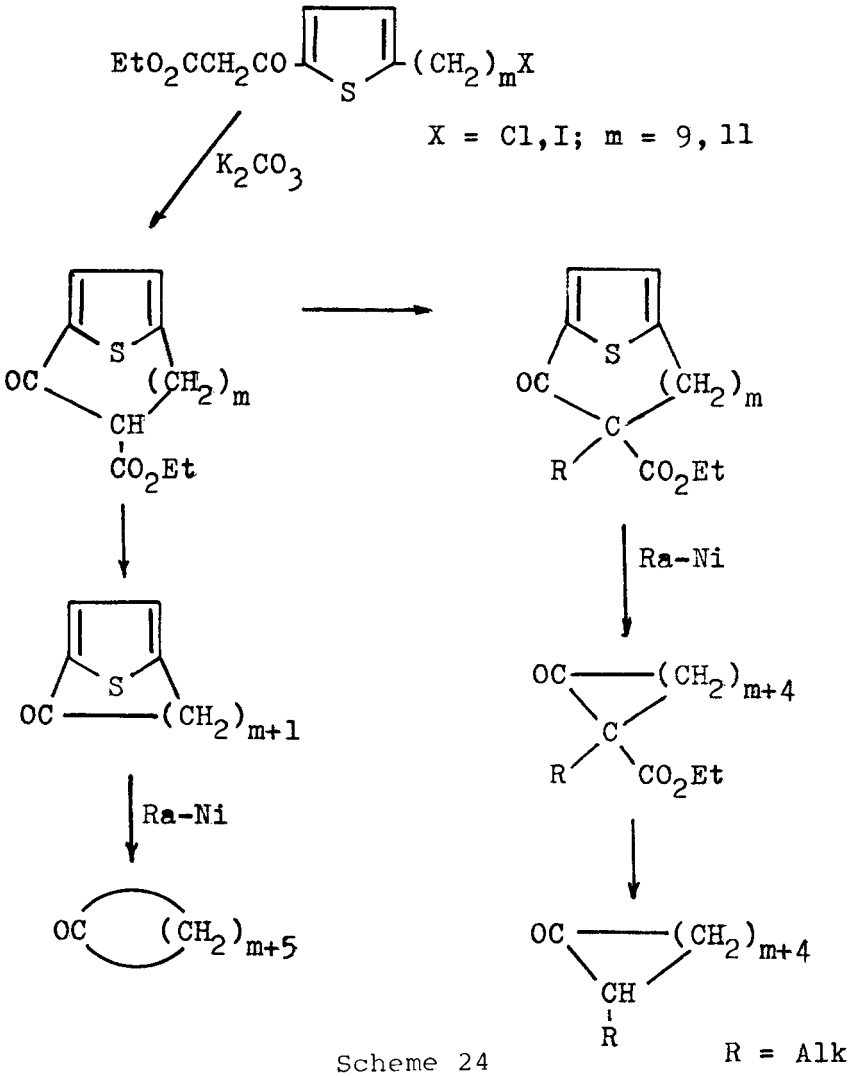


Scheme 23

of cyclization products (Scheme 23). Later the same group [141,142] described the synthesis of macrocyclic ketolactones that possess benzene and thiophene rings. The action of Raney nickel on these compounds leads to ketolactones with a skeleton related to that of the natural macrolide zearalenone, but, to a large extent, the products of partial or complete reduction of the keto group are also formed (Scheme 23).

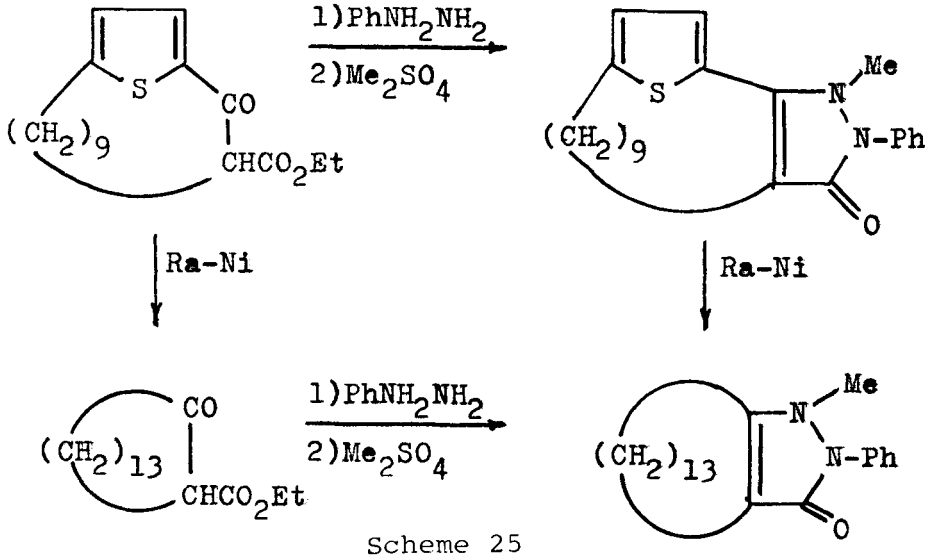
Another route to the higher alicyclic compounds was elaborated by Taits, Gol'dfarb et al. It consists in the intramolecular alkylation of ω-halo-β-ketoesters with subsequent "ketonic hydrolysis" and reductive desulfurization. For the preparation of the starting compounds thiophene, ω-chloroalkanoic acids and monoethyl malonate chloride were used. By this route cyclopentadecanone (exaltone) and cycloheptadecanone (dihydrocivetone) were obtained [143,144]. The alkylation of the unsubstituted ketoesters allowed to obtain alicyclic alkyl-substituted ketoesters and then α-alkylcycloalkanones [145] (Scheme 24).

The study of the conditions and kinetics of 2-(9-iodononyl)-5-(ethoxycarbonylacetyl)thiophene cyclization over potassium carbonate as well as the effect of carbonates of other alkali metals [146-148] demonstrated the role of the carbonate surface in this reaction. When the same cyclization was carried out in homogeneous medium (in the presence of potassium tert.-butylate) [149] the maximum concentration of the iodide was determined at which intermolecular reaction leading to by-products does not take place; this is essential for the preparative use of the cyclization.



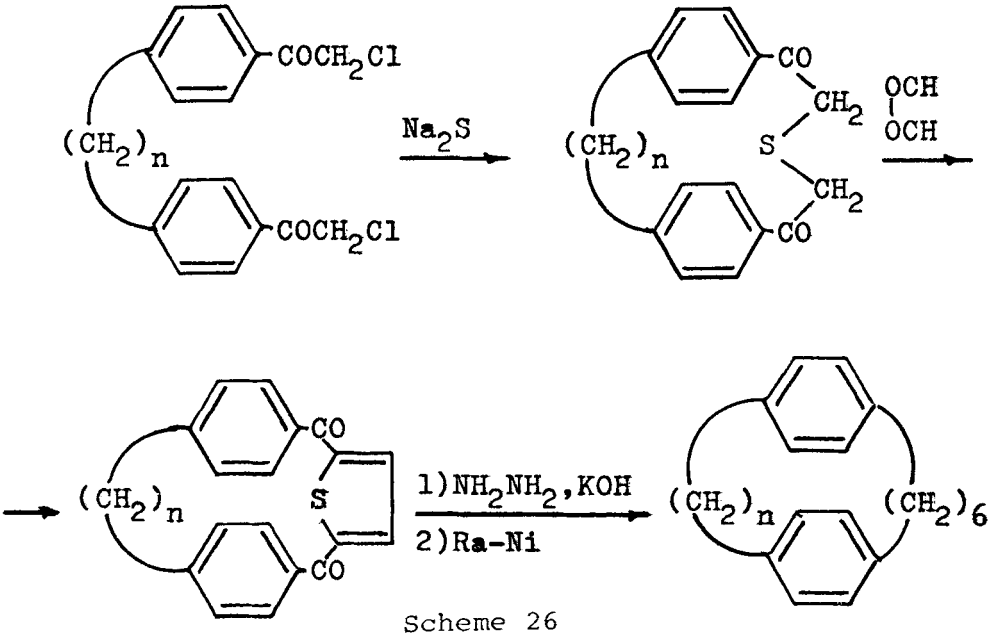
Scheme 24

Starting with macrocyclic β-ketoesters possessing a thiophene ring, Gol'dfarb, Taits and Krasnyanskaya succeeded recently in the synthesis which uses reductive desulfurization for the preparation of many-membered pyrazolone derivatives [15o] (Scheme 25).



Scheme 25

A new interesting synthesis of macrocyclic systems possessing one thiophene and two benzene rings was described by Miyahara, Takahiko and Yoshino [151]. The reductive desulfurization of these systems leads to /n,6/-paracyclophanes (Scheme 26).



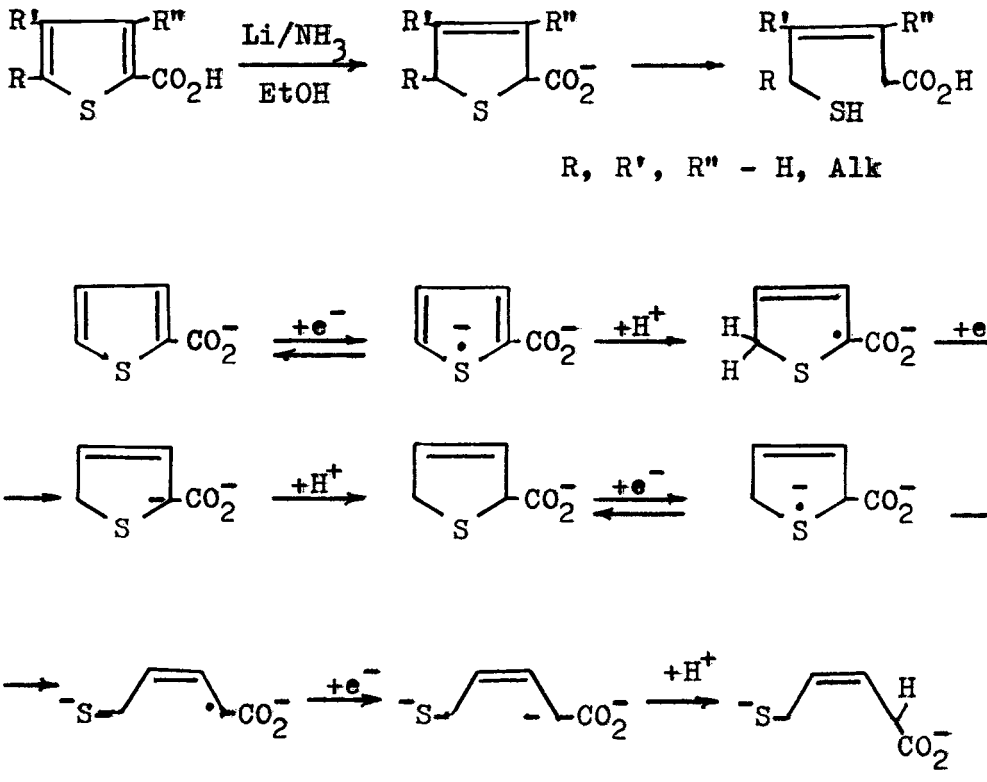
Scheme 26

REDUCTION WITH ALKALI METALS IN LIQUID AMMONIA

Reduction of thiophenes with alkali metals in liquid ammonia may lead to various products: dihydrothiophenes, unsaturated mercaptans and sulfur-free compounds. As it was shown in the first investigations [8-10, 152-156], the reaction conditions - the nature of the metal and the presence of a proton donor and its efficiency - substantially influence the results of the process. At present sufficiently selective procedures have been elaborated for reductive cleavage of thiophene rings with alkali metals in liquid ammonia.

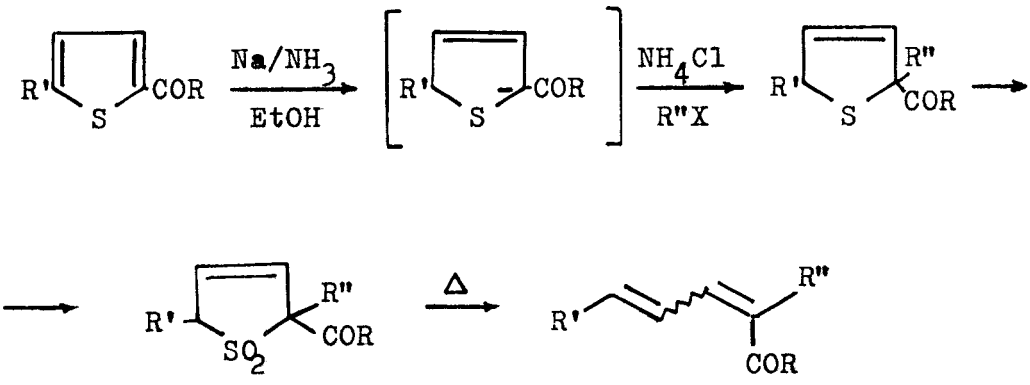
The reduction mechanism consists in consecutive additions of solvated electrons and protons to the aromatic or heteroaromatic substrate [154,156]. In accordance with this mechanism the presence of electron-withdrawing substituents facilitates the reduction. The primary products of the reduction are dihydrothiophenes, but their isolation is hindered as a rule by the presence of other substances formed in further transformations leading to the ring cleavage [157,158]. Preparative isolation of 3- and 5-methyl-2,5-dihydro-2-thiophenecarboxylic acids was described by Blendermann et al.[159] who treated lithium salts of thiophenecarboxylic acids with 2 eq. lithium in liquid ammonia without an alcohol added.

The ring cleavage proceeds effectively when an excess of alkali metal is used and this allows to prepare some compounds which are hardly available by other routes. When studying the reactions of 2-thiophenecarboxylic acid and its 3-, 4- and 5-methyl-substituted derivatives with 5 eq. lithium in liquid ammonia in the presence of ethanol Gol'dfarb et al. [157,160] demonstrated a regio- and stereospecific reductive cleavage that resulted in Z-isomers of the corresponding β,γ-unsaturated δ-mercapto acids (Scheme 27).



Scheme 27

In light of the mechanism shown above it is quite easy to understand the interesting results [161] on the reductive alkylation of 2-acylthiophenes and 2-thiophenecarboxylic acid. In this case, the action of sodium in liquid ammonia was carried out in the presence of a proton donor (ethanol) and was followed by treatment of the mixture with ammonium chloride and then with 2-4,5 eq. of an alkylating reagent. Oxidation of the resulting 2,5-dihydrothiophenes into sulfones and pyrolysis of the latter made it possible to prepare a number of alkyl alkadienyl ketones (Scheme 28).



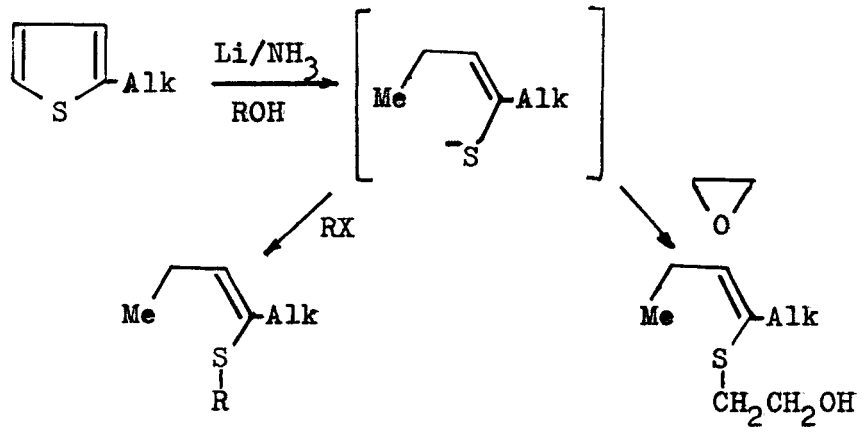
R = OH, Alk, cyclo-Alk; R' = H, Alk;
R" = Alk, $PhCH_2$, CH_2=$CHCH_2$

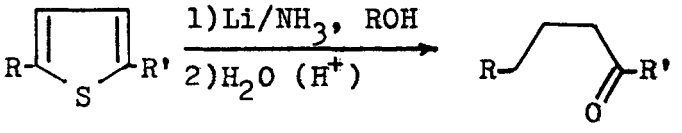
Scheme 28

Substituted unsaturated mercaptans, which are formed during the cleavage of the thiophene ring, can be reduced under the action of solvated electrons with the formation of hydrogen sulfide and unsaturated substances that do not contain sulfur. Furthermore, these mercaptans, or more precisely the corresponding thiolate anions, are capable of nonreductive transformations with retention or loss of the sulfur atom.

Gol'dfarb and Zakharov demonstrated that 2-alkylthiophenes give α,β-unsaturated sulfides by the action of lithium in liquid ammonia followed by the treatment with alkyl halide or ethylene oxide [162-164] (Scheme 29).

When the mixture formed by the action of lithium in liquid ammonia on alkylthiophenes underwent hydrolysis, dialkylketones were obtained in 45-75% yields [165]. In the case of thiophene itself a small amount of butyraldehyde was formed, which was identified as the semicarbazone. Under the same conditions, ω-(2-thienyl)alkanoic acids were converted into aliphatic ketoacids [165,166], ω-(2-thienyl)alkanols give ketoalcohols [167] and 2-(ω-dialkylaminoalkyl)thiophenes are converted into the corresponding aminoketones [168] in 70-80% yields (Scheme 29).

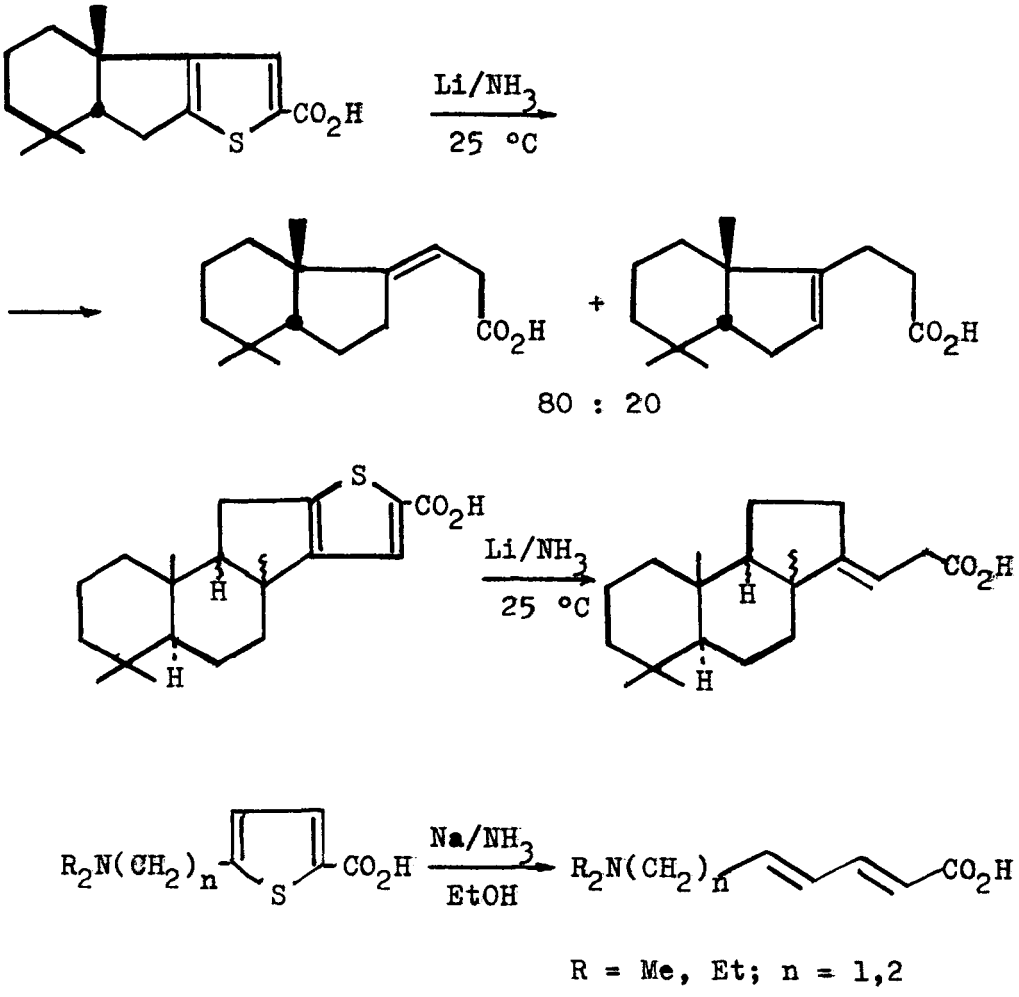




R = H, Alk;
R' = Alk, $(CH_2)_nY$;
Y = CO_2H, OH, $NAlk_2$; n = 1-9

Scheme 29

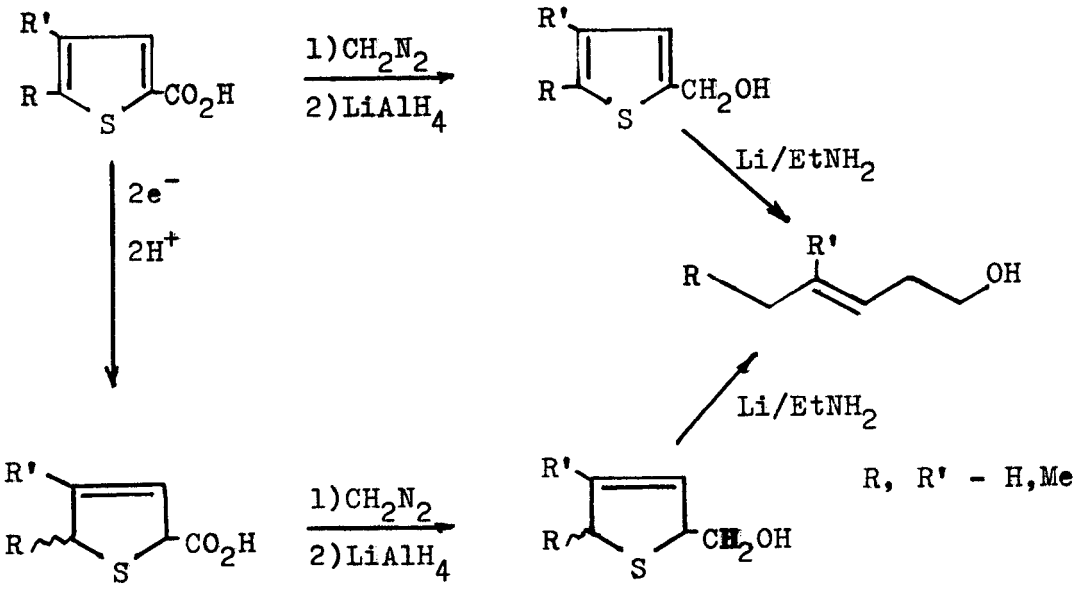
In some cases, substituted thiophenecarboxylic acids and thienylcarbinols undergo hydrogenolysis of the C-S bond under conditions of reductive cleavage and products that do not contain sulfur are formed. Such transformations are described by Semenovskii and Emel'yanov for the tri- and tetracyclic acids when lithium was used in liquid ammonia at 25°C under pressure [169,170] (Scheme 30). In the case of reductive cleavage of 5-dialkylaminoalkyl-2-thiophenecarboxylic acids, Zakharov, Gold'dfarb and Stoyanovich observed regio- and stereoselective formation of ω-dialkylamino E,E-alkadienecarboxylic acids [171] (Scheme 30).



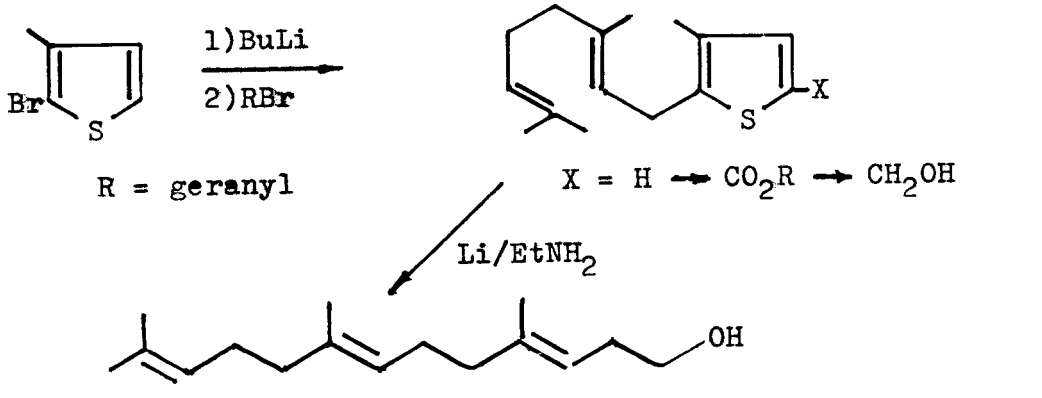
Scheme 3o

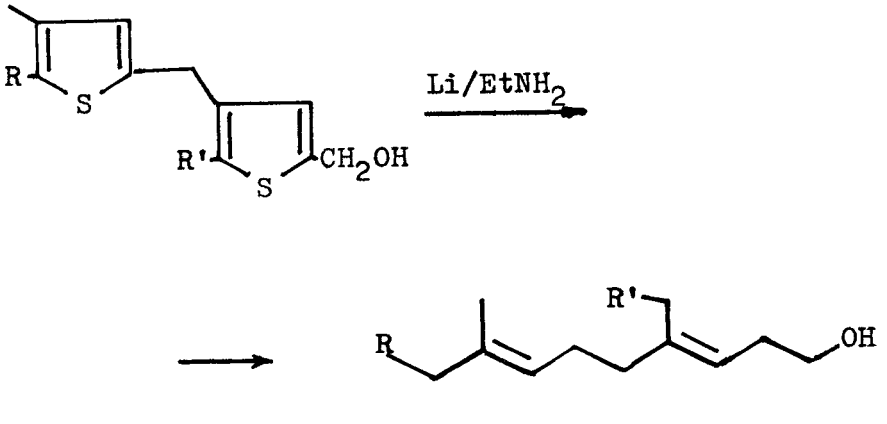
For the stereoselective synthesis of E-homoallyl carbinols from thienyl- and dihydrothienylmethanols Lozanova, Moiseenkov and Semenovskii used successfully the action of lithium in ethylamine [172-174] (Scheme 31).

The use of the same reagent allowed E,E-homofarnesol to be prepared via thiophene derivatives [175] as well as homogeraniol and some of its homologues to be obtained from the dithienylmethane derivative [176] (Scheme 32).



Scheme 31





Scheme 32

CONCLUSION

The methods considered for transformations of thiophenes into compounds of other series reveal diverse uses of thiophene and its derivatives in organic synthesis. In this connection it is of great value that thiophene belongs to the rather small group of heterocycles having rich sources of raw materials. Light fractions of coal and shale tars are among these materials. Another important source is the catalytic synthesis of thiophene and its homologues from petroleum hydrocarbons and simple inorganic sulfur compounds. These catalytic processes allow to transform a hydrocarbon into heteroaromatic thiophene systems which can be functionalized without difficulty and finally cleaved giving various functional derivatives of the starting hydrocarbon. Thus, one can say that thiophene occupies an unique position among accessible heteroaromatic systems, because it is possible not only to obtain its own derivatives, but also to use thiophene itself as a powerful tool in the synthesis of various compounds belonging to other series.

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