METHODS FOR THE SYNTHESIS OF 2-AMINOTHIOPHENES AND THEIR REACTIONS (REVIEW)

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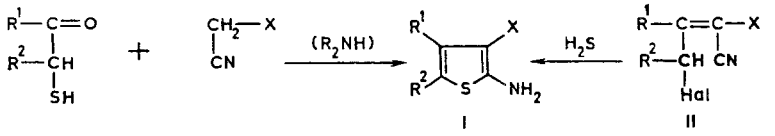
2-Aminothiophenes are readily formed as a result of various cyclization reactions. The method of preparation of derivatives of 2-aminothiophene-3-carboxylic acids and 2-amino-3-acylthiophenes from carbonyl compounds, nitriles that have an active methylene group, and sulfur is particularly simple and rich in possibilities. The aminothiophenes can be converted to other thiophene derivatives and used primarily for the preparation of condensed thiophenes such as thionaphthenes, thienopyrroles, thienothiazoles, thienoisothiazoles, thienopyrimidines, thienopyridines, and thienodiazepines.

Synthetic Methods

2-Aminothiophene was first obtained by Stadler by reduction of the nitro derivative, but the free base proved to be unstable [1]. In addition to methods involving reduction, cleavage of azides, rearrangement of oximes and aminolysis of activated 2-halo- [2, 3] or 2-mercaptothiophenes [4], cyclization reactions that lead directly to 2-aminothiophene have recently been used [3, 5, 6]. It was found that 3- or 2-aminothiophenes that have electron-acceptor groups in the 3 or 5 position (for example, 2,5-diamino-3,4-dicyanothiophene, obtained from tetracyanoethylene and H_2S [7]) are extremely stable. Thus cyclization of tertiary amides of phenylthioacetic acid with phenacyl bromides leads to substituted dialkylaminothiophenes [8]. The latter are also obtained from dialkylamides of 2,4-pentadienecarboxylic acid [9]. N-Substituted or N-acylated 2-aminothiophenes [10, 11] are also formed from α-halo carbonyl compounds and N-substituted α-cyanothioamides [10, 11] or enaminothioamides [12, 13], as well as by intermolecular cyclization of α-chlorothioacetanilides [14]. Another elegant method for the synthesis of nitrogen-unsubstituted 2-aminothiophene consists in the rearrangement of β-cyano-substituted 5-ethylidenerhodanines [15], and, finally, the parent compound itself of the series is formed as a result of acid cyclization of γ-(benzylmercapto)crotononitrile [16, 17]. The rearrangement of rhodanines mentioned above also includes cyclization of the nitrile, and 2-aminothiophene-3,5-dicarboxylic acids or their esters, as well as 2-amino-3-benzoylthiophene-5-carboxylic acids; compounds related to the I type under discussion here, have become accessible by means of it.

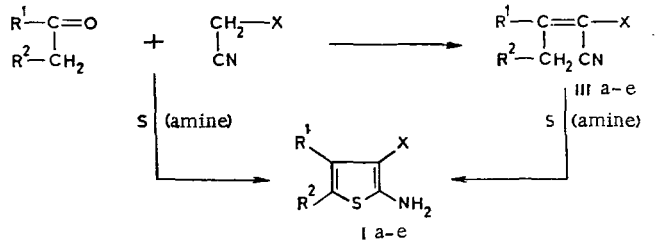
As we observed sometime ago [18, 19], an easily modifiable method for the synthesis of 2-aminothiophenes I that have an electron-acceptor grouping in the 3 position consists in the base-catalyzed reaction of α-mercapto ketones and aldehydes with nitriles with an active methylene group in the α position. The first step in the reaction, which gives the products in good yields even at room temperature, is probably addition to the nitrile group, after which Knoevenagel condensation follows. Alcohol is usually employed as the solvent, but the reaction of malononitrile with mercaptoacetone, for example, can also be carried out in water. It is important that thiophenes I with free 4 and 5 positions can also be obtained by this method. In some cases compounds of the I type are also formed from γ-halocrotononitriles II [18, 19], but in a preparative respect this method is of interest only in certain special cases.



R = H, alkyl; X = CN, CO_2R, $CONH_2$, COAr, $C_6H_4NO_2$-p, SO_2R

Chemistry Faculty, Dresden Technical University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1299-1315, October, 1976. Original article submitted April 12, 1976.

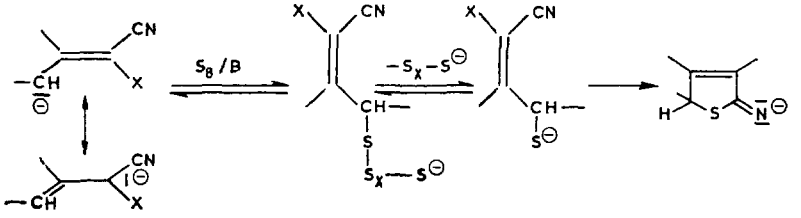
Somewhat later it was found that thiophenes of the I type can be obtained by a considerably simpler method: carbonyl compounds with a sufficiently reactive C=O group that have a methylene grouping in the α position react with the appropriate nitriles and sulfur in the presence of bases and also give 2-aminothiophenes I [20-22]. Morpholine, diethylamines, and triethylamine can be used as the bases. Sometimes one initially specially prepares alkylidene derivative III, which is then subjected to reaction with sulfur [20, 21]. However this method must be used only in the case of aryl ketones (R^1 = Ar) with low reactivities, since in general it rarely has any advantages.



R^1 = alkyl, aryl, H; $R^1-R^2 = -(CH_2)_n-$; R^2 = H, alkyl, aryl, COR, $CO_2C_2H_5$ ($R^1 = R^2 \neq H$)

I, III a X = CN; b X = CO_2R; c X = $CONH_2$; d X = COAr; e X = SO_2R

This reaction, which has been confirmed [23, 24] and expanded (for example, see [25-32] in the research of other investigators, is similar to the Asinger reaction [33]. Although α-mercapto carbonyl compounds or β-mercapto enamines >N−C=C−SH could also be formed here as intermediates, we nevertheless propose [34] that the reaction proceeds through a step involving the formation of nitrile III:



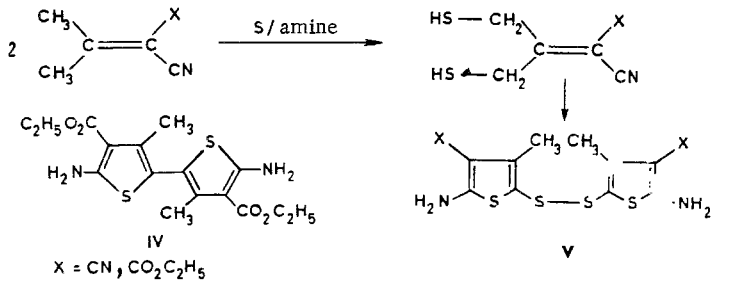
Irreversible cyclization follows reversible "thiolation" as a result of which the reaction does not stop even in the case of a negligible carbanion concentration.

The corresponding enamines [35] can be used in place of carbonyl compounds, and this facilitates the condensation step leading to the formation of nitrile III. This sometimes may prove to be useful in a preparative respect; for example, desoxybenzoin can be converted to an aminothiophene of the I type by this method. Cyclohexanethione has also been used in place of cyclohexanone in this reaction [36].

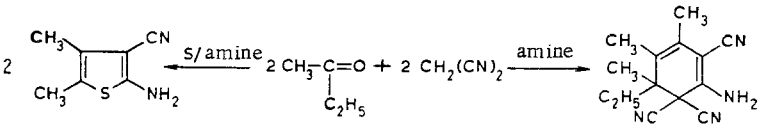
Alcohol is the most convenient solvent, whereas dimethylformamide (DMF) is the most convenient solvent in the case of aldehydes. The optimum reaction temperature is 25-50°C, whereas the optimum temperature for less reactive components such as cyanoacetamide and β-dicarbonyl and aryl-substituted compounds III (R^1 = Ar) is 70-90°; in the latter case the yields reach 85% (the yields indicated in [20, 21] can be substantially raised in a number of cases).

The structure of the carbonyl compound can be widely varied. The only thing of importance is that it should be able to undergo (intermediate) Knoevenagel condensation, during which isolation of the product of condensation of III is entirely unnecessary in each case. For example, this occurs in the case of acetonylacetone [37], which additionally gives dithienyl IV [38] (the primary reaction pathway here is thiolation rather than the other basecatalyzed reactions). Yet another limitation is illustrated by the fact that acetaldehyde does not react to give thiophene I nor through a step involving nitrile III, but rather undergoes aldol condensation, which in this case turns out to be the dominant pathway. Acetone or its ylidene derivative III undergoes bisthiolation, as a result of which disulfide V was obtained [39] [nevertheless, aminothiophenes I (R^2 = H) are formed from aryl methyl ketones as well as, for example, from isopropyl methyl ketone].

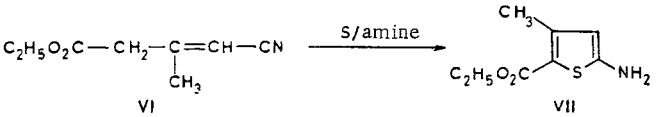
The methylene groups are preferably thiolated, so that practically only 4,5-dimethylthiophene I ($R^1 = R^2 = CH_3$) was isolated in the case of methyl ethyl ketones. To obtain 4-alkylthiophenes I with R^2 = H, however, removal of the 5-carbethoxy groups (see next page) is used in addition to a reaction proceeding through a step involving the formation of oxomercaptans.



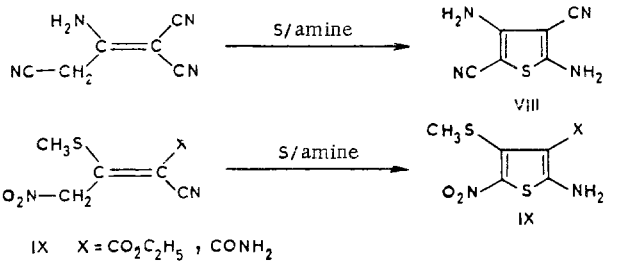
The limitations of the synthetic method with respect to the nitrile component are not determined only by the activity of its methylene group. It is known that ylidene malononitriles III are inclined to undergo base-catalyzed dimerization [40], which in this case completes with thiolation. Aldehydes, as well as aryl ketones, therefore do not form thiophenes Ia on reaction with malononitrile and sulfur, whereas in the case of methyl ethyl ketone the competitive reaction can be suppressed at 20-30° by maintaining the amine concentration constant. (However, cyclohexanone, acetoacetic ester, and benzylacetone, for example, are smoothly converted to o-aminonitriles Ia [40]).



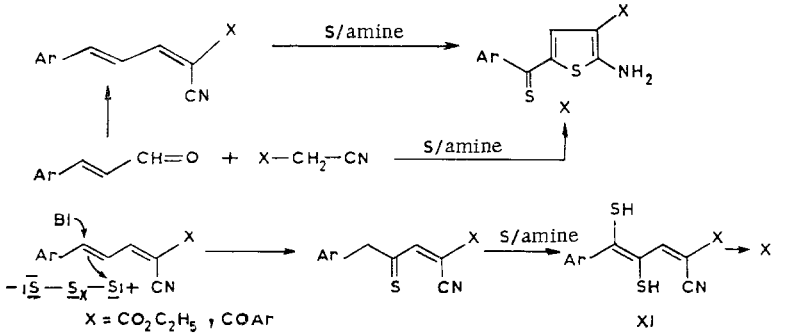
Up to now, cyanoacetic acid derivatives, acylacetonitriles, sulfonylacetonitriles [31, 34], and (2-thiazolyl)-acetonitrile [41] have been used as the nitrile component. Benzyl cyanide does not react through a step involving the formation of nitrile III. The electron-acceptor X grouping III that is necessary for successful cyclization can be located not only in the 2 position but also in the 4 position. Thus nitrile VI – the product of condensation of cyanoacetic acid with acetoacetic ester – is smoothly converted [42] to thiophene VII with a free 3 position.



Furthermore, aminothiophenes can also be obtained from those compounds of the III type that are formed by a method that differs from Knoevenagel condensation. Malononitrile dimer reacts to give 2,4-diaminothiophene VIII [43], whereas substituted γ-nitrocrotononitriles give 2-amino-5-nitrothiophenes IX [44].

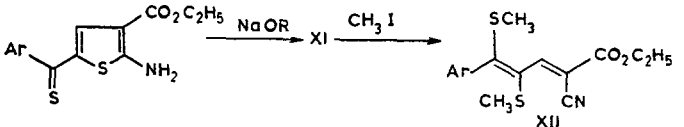


The reaction of cinnamaldehyde with nitriles and sulfur [45, 46] which leads to 2-amino-5-thioaroylthiophenes X, has been described. Compound XI is considered to be an intermediate. It might be assumed that sulfur initially enters the γ position, and the resulting thione (or enethiol) immediately undergoes α-thiolation to give dithiol XI.



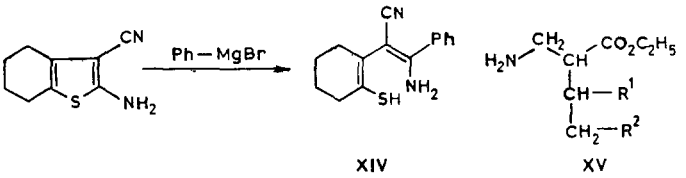
Reactions with Ring Cleavage

2-Amino-5-thioaroylthiophenes X are cleaved even under mild conditions by alkoxide to give enedithiol XI, methylation of which leads to stable bis(methylthio)cinnamylidenecyanoacetic ester XII [45, 46].



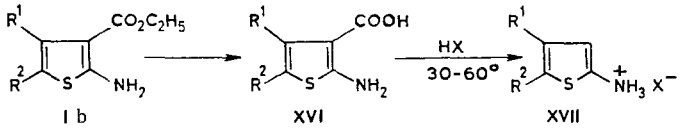
XIII a $R^1 = CH_3$; $R^2 = H$; b $R^1 = C_6H_5$, $R^2 = H$; c $R^1 = CH_3$, $R^2 = COCH_3$; d $R^1 = CH_3$, $R^2 = CO_2C_2H_5$

Under more severe conditions sodium alkoxide also cleaves o-amino ester Ib, but here the product easily undergoes recyclization to give 2-hydroxy-3-cyanothiophene XIII [47]. The reaction proceeds smoothly only if the 5 position is free or substituted by an electron-acceptor grouping. Thiophenes of the XIII type with a free nucleophilic 5 position can be used for subsequent reactions. Phenylmagnesium bromide also cleaves o-aminonitrile Ia [R^1-R^2 = $(CH_2)_4$-] to give, as a result of addition to the eneamino group, mercapto dieneamine XIV [48]. The latter is stable in the crystalline state, but undergoes cyclization in solution or at high temperatures to give an aminothiophene or, with splitting out of hydrogen sulfide, to give a pyrrole. Finally, desulfuration, which is widely used for other thiophenes [49], can be used for the preparation of esters of α-substituted β-amino acids XV from aminothiophenes Ib (preliminary acetylation is recommended here) [34]. The thiophene ring was cleaved by an analogous method [50-52] in the synthesis of some pyrimidines from condensed systems obtained on the basis of compounds of the I type.



Decarboxylation of 2-Aminothiophenecarboxylic Acids

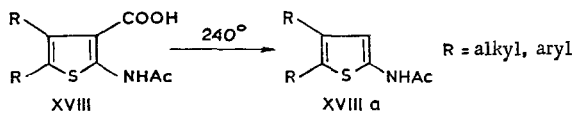
Although esters Ib, in contrast to anthranilic acid esters, under normal conditions do not undergo aminolysis or hydrazinolysis, they can be saponified to stable 2-aminothiophene-3-carboxylic acids XVI. The latter are decarboxylated in the presence of oxalic or hydrochloric acid to give 2-aminothiophenes XVII, during which one observed initial precipitation of stable salts, from which, however, the free bases can be readily isolated [42, 53, 54]. Free aryl-substituted amines XVII are stable, whereas the alkyl-substituted amines undergo decomposition after a certain time even when they do not have access to air (2-aminothiophene itself still could not be obtained in acceptable yield by this method). Amine XVII can also be condensed to give an oxazine (see below).

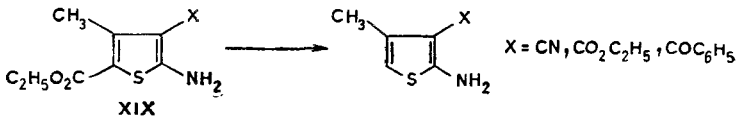


R^1, R^2 = H, alkyl, aryl

Another variant of decarboxylation is based on the use of N-acylamino acids XVIII, which lose CO_2 only at 240° [55].

Saponification (partial) of ester XIX leads to thiophenes with a free 5 position, which are also formed as a result of thiolation of acetoacetic ester [34].

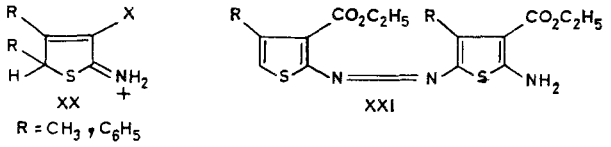




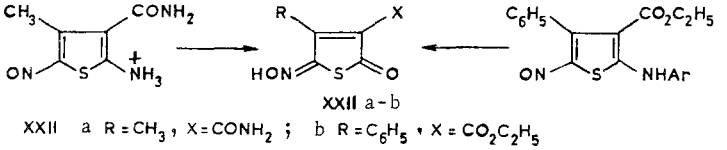
Reactions at the Amino Group

Thiophenes of the I type are weak bases and upon protonation, which occurs in the 5 position to give XX, behave like enamines [56]. Despite this, they undergo, although with a certain amount of difficulty, the usual reactions of amines, including the addition of carbon disulfide [57]. Up until now, many reactions have been used only as intermediate reactions for the construction of 2,3-condensed systems (see below). A number of acylation reactions have been realized in order to obtain pharmacologically active preparations; in particular, the acylation of 2-amino-3-aroylthiophenes Id has been developed [58-67].

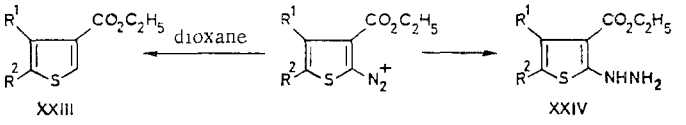
Diazotization naturally occupies a special position; it proceeds with a certain amount of difficulty in the case of nitriles Ia but takes place smoothly in the case of esters Ib. In this case, aminothiophenes with a free 5 position immediately undergo self-coupling to give azo derivatives XXI (this is also observed when the 3 position is free) [38].



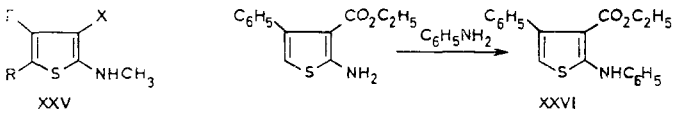
Nitrosation also occurred in the case of amide Ic ($R^1 = CH_3$), since oxime XXIIa was obtained after hydrolysis [68]. If the amino group of ester Ib ($R^1 = C_6H_5$) is acylated, C-nitrosation is also realized, and oxime XXIIb is formed in good yield after hydrolysis.



However, when the 5 position is occupied, diazotization with subsequent "self-coupling" is impossible. Thus azo dyes with high fastness to light that contain an aminothiophene I residue as a diazo component have been described [69, 70]. The reductive deamination of the diazotized amino ester in dioxane leads to thiophene-3-carboxylic acid ester XXIII in 30-60% yield [71]. Finally, some diazonium salts can be reduced to 2-hydrazinothiophenes XXIV [72].

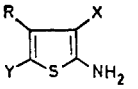


The reduction of ethoxymethyleneamino derivatives with sodium borohydride has been recommended for the monomethylation of amines of the I type to secondary amines XXV [73, 74]. Monoalkylation can also be realized by reaction of N-acylaminothiophenes with halo derivatives [75-77]. Up until now, replacement of the amino group has been observed only in the case of Ib ($R = C_6H_5$), which reacts with aniline hydrochloride at 180° to give amine XXVI [38].



Reactions in the Thiophene Ring

Aminothiophenes I with a free 5 position undergo the electrophilic substitution reactions normal for aromatic compounds and known for other thiophenes; in the general case, protection of the amino group is not obligatory (for example, see [31, 69]). In addition to the readily occurring acylation, iodination, and Vilsmeier reaction, mercuration to give 5-chloromercuri and 5-acetomercuri derivatives XXVIIa can be effected [20, 34]. Free amines can also be vinylated by tetracyanoethylene to give XXVIIb and can also be oxidatively thiocyanated to give derivatives of the XXVIIc type [78]. The ability of thiophenes I ($R^2 = H$) to undergo diazo coupling to give azo dyes XXVIIe was subsequently studied in detail [79].



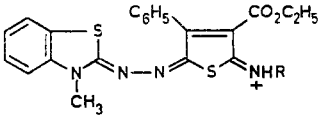
XXVII a-e

R = alkyl, aryl ; X = $CO_2C_2H_5$, CN, $CONH_2$, COAr

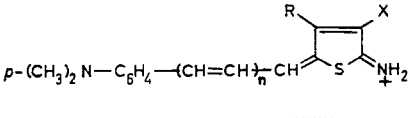
a Y = HgAc ; b Y = $C(CN)=(CN)_2$; c Y = SCN ;

d Y = CH_2NR_2 ; e Y = $ArN=N$

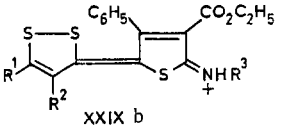
Cationic dyes XXVIII were obtained as a result of Hunig coupling. Like dialkylaminothiophenes [80, 81], compounds of the I type ($R^2 = H$) undergo the Erlich reaction to give violet thienylarylmethines XXIXa. In the presence of $AlCl_3$, 3-chlorodithiolium salts [82] also react to give XXIXb rather than products of reaction at the amino group [38].



XXVIII



XXIX a

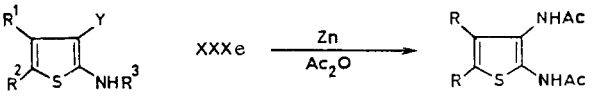


XXIX b

XXVIII R = H, C_6H_5 ; XXIX a n = 0,1 ; R = H, CH_3, C_6H_5 ; X = $CO_2C_2H_5$, CN

XXIX b $R^1 = C_6H_5$, Cl ; $R^2 = H, C_6H_5$; $R^3 = H, C_6H_5$

As expected, the free 3 position in thiophenes VII, XVII, and XVIIIa is less nucleophilic. However (when the 5 position is occupied), they can be formylated to give aldehydes XXXa [83], oxidatively thiocyanated to give derivatives XXXb [38, 84], and aminomethylated to amines XXXc [85]. Sulfur chlorides react with N-acetylated amines XVIIIa to give sulfides and disulfides [86] and with sulfenyl chlorides to give sulfides XXXd [87]. 3-Arylazothiophenes XXXe, formed as a result of diazo coupling, can be reduced in the presence of acetic anhydride to 2,3-di(acetamido)thiophenes XXXI [88].



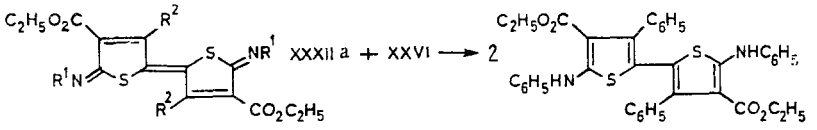
XXX a-e XXXI

R^1 = H, alkyl, aryl ; R^2 = alkyl, aryl, $CO_2C_2H_5$

XXX a R^3 = Ac, Y = CHO ; b R^3 = H, Y = SCN ; c R^3 = Ac, Y = CH_2NR_2 ;

d R^3 = Ac, Y = ArS ; e R^3 = H, Y = $ArN=N$

The ability of thiophenes I with a free 5 position to undergo oxidation is reflected in the appearance of the violet color of solutions containing oxygen. The very first studies showed that dehydrodimerization to give a C–C bond occurs during oxidation [38]: 2-anilinothiophene XXVI is oxidized in analogy with the corresponding thiazole [89] to give bis($\Delta^{5,5'}$-3-thiolenon-2-imine) XXXIIa, which gives dithienyl XXXIII on reduction or disproportionation with starting XXVI. N-Bromoimino derivative XXXIIb was obtained from free amino ester Ib ($R^1 = C_6H_5$) and bromine in glacial acetic acid, whereas the formation of imine XXXIIc was proved in the oxidation of Ib ($R^1 = CH_3$).

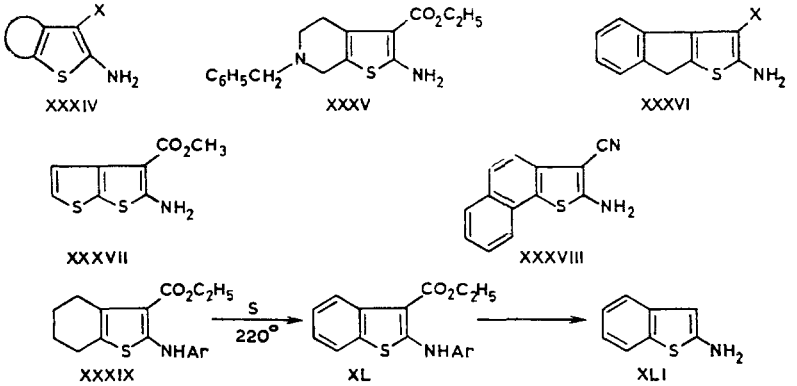


XXXII a-c

XXXII a $R^1 = R^2 = C_6H_5$; b $R^1 = Br$, $R^2 = C_6H_5$; c $R^1 = H$, $R^2 = CH_3$

4,5- and 3,4-Condensed 2-Aminothiophenes

4,5-Condensed 2-aminothiophenes are obtained from cyclic ketones. Not only carbocyclic ketones [20, 27, 90], particularly tetralone [26, 34], but also heterocyclic ketones, including 4-piperidone [90, 91], quinuclidone [92], 4-thiacyclohexanone [26, 90, 93], and dithiacycloheptanone [94. 95], have been subjected to the reaction in order to obtain pharmacologically active preparations such as, for example, "tinoridin" XXXV ("nonflamin," Yoshitomi, Japan) (see [96] and the literature cited therein). Indenothiophenes XXXVI were obtained from 1-indanone [34, 97]. Some of these systems can be aromatized by dehydrogenation (for example, with sulfur) or dehydrohalogenation. Thus thieno[2,3-b]thiophene XXXVII was synthesized from cyclopentanethione [98], and benzo[g]thionaphthene XXXVIII was synthesized from β-tetralone [98]. 4,5-Tetramethylenethiophene XXXIX is dehydrogenated in dimethyl phthalate to give benzo[b]thiophene XL in 85% yield, from which free 2-aminothionaphthene XLI was obtained [100, 101].

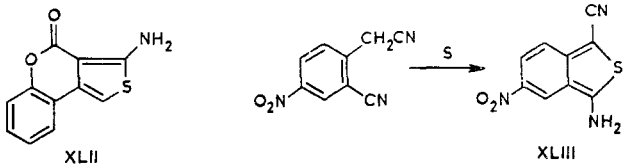


XXXIV XXXV XXXVI

XXXVII XXXVIII

XXXIX XL XLI

Up until now, 3,4-condensed 2-aminothiophenes have been synthesized only as a result of thiolation of the appropriate components. 3-Aminothieno[3,4-c][1]benzopyran-4-one (XLII) was obtained from 4-methylcoumarin-3-carbonitrile, synthesized from o-hydroxyacetophenone and cyanoacetic ester in the presence of sulfur at 60°. At lower temperatures, the 1,1'-disulfide is formed along with it as a result of dithiolation [102]. 2-Cyano-4-nitrobenzyl cyanide reacts with sulfur to give substituted 1-aminobenzo[c]thiophene XLIII [103].

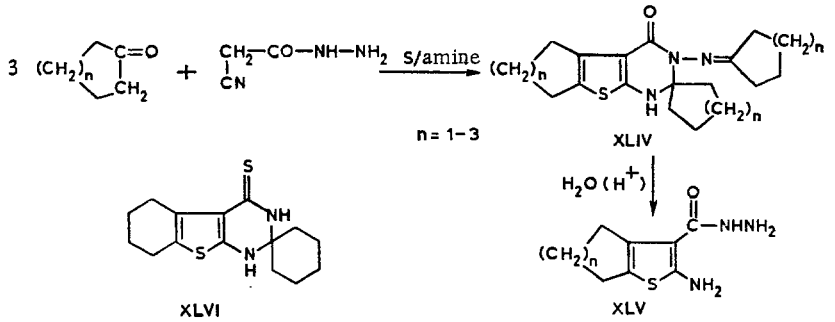


XLII XLIII

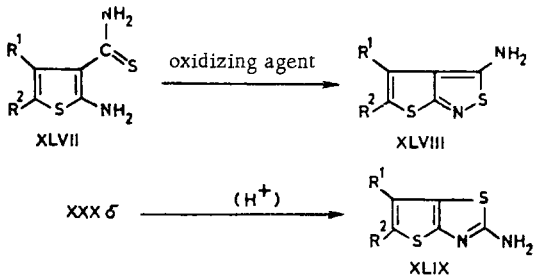
2,3-Condensed Thiophenes

Aminothiophenes of the I type are o-aminocarbonyl compounds that, like their benzene analogs, can be used for the preparation of numerous 2,3-heterocondensed thiophenes by known methods. Many of the syntheses that have been described up until now have been carried out in order to search for new pharmacologically and biologically active compounds (see also [6]).

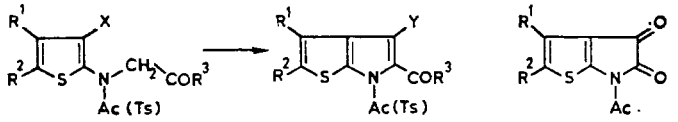
A 2,3-condensed compound can be formed even if the carbonyl derivative undergoes a secondary reaction under mild conditions. Thus in the reaction of cyanoacetylhydrazide with sulfur and cyclic ketones one observes the immediate formation of dihydrothieno[2,3-d]pyridone derivative XLIV, from which the free hydrazide (XLV) of 2-aminothiophene-3-carboxylic acid is obtained by hydrolysis [10, 14] (the hydrazide is not obtained as a result of hydrazinolysis of ester Ib). Cyanothioacetamide also reacts similarly with cyclic ketones and sulfur to give, for example, dihydrothienopyrimidinethione XLVI with cyclohexanone [34].



The cyclizations discussed below are similar to the known reactions in the benzene ring, but one must take into account the fact that the reactivities of carbonyl compounds of the I type are generally lower than those of benzene derivatives. Thus nitriles Ia add hydrogen sulfide only under pressure [42] to give thioamides XLVII, which can also be obtained from α-oxo mercaptans and cyanothioacetamide [105]. o-Aminothioamides XLVII are smoothly oxidized to 3-aminothieno[2,3-c]isothiazoles XLVIII [42, 106]. The isomeric 2-aminothieno-[2,3-d]thiazoles XLIX were synthesized by the above-mentioned oxidative thiocyanation through a step involving the formation of compounds of the XXXb type, which undergo partial cyclization during the synthesis or upon acid catalysis [41, 44, 84].



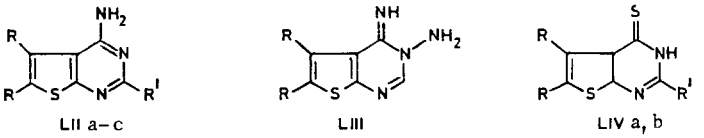
3-Amino- and 3-hydroxythieno[2,3-b]pyrroles L were obtained as a result of alkylation of N-acylated or N-tosylated thiophenes Ia, b with α-halo carbonyl compounds and subsequent Thorpe cyclization or Dieckmann condensation [76, 77]. Thieno[2,3-b]pyrrolinediones LI are formed from N-acetylated thiophenes XVIIa and oxalyl chloride [107].



L Y = NH_2, OH ; R^1 = alkyl, C_6H_5; R^2 = H, alkyl ; R^3 = OC_2H_5, $N(C_2H_5)_2$

LI R^1 = H, alkyl, aryl ; R^2 = alkyl, aryl, $CO_2C_2H_5$

Thieno[2,3-d]pyrimidines are readily obtained from aminothiophenes Ia-d (see also the above). 4-Amino-thieno[2,3-d]pyrimidines LII* were synthesized from o-aminonitriles by various methods: LIIa was synthesized from amine Ia and formamide [34] or by successive treatment with an ortho ester and ammonia [30, 40, 79, 108] (hydroxyamine LIIb is also known in the form of its N-substituted derivatives [30, 108]). If hydrazine is used in place of ammonia in this case, one obtains LIII, which, being an o-diamine, can be subjected to subsequent condensation [74]. In addition, 2-substituted 3-N-oxides of the LIIa type can be synthesized from N-acylated amines Ia and hydroxylamine [109]. Hydroxy amine LIIb is formed from Ia and urea [40], whereas the reaction of Ia with formamidine hydrochloride leads to diamine LIIc [26, 27, 90]. Thienopyrimidinethione LIVa was obtained from amine Ia and thioamides [40, 110], whereas dithiones LIVb were obtained from xanthates and Ia [111].

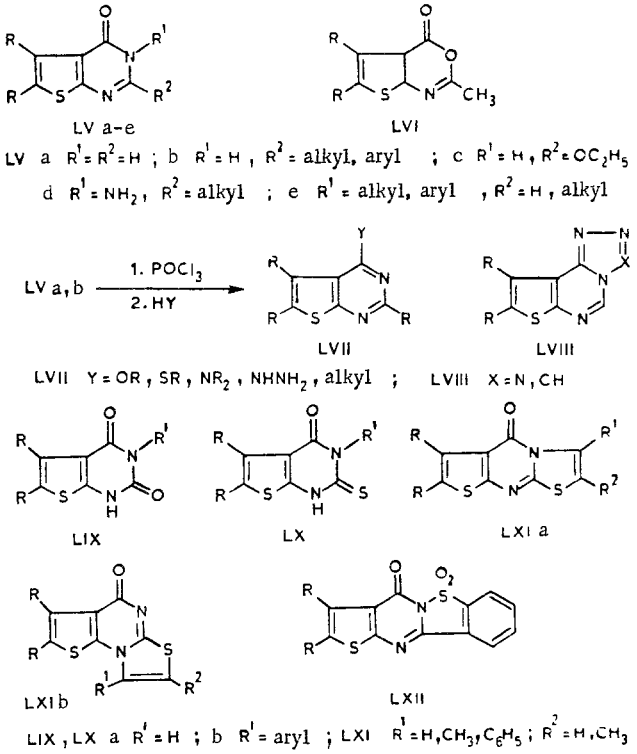


LII a R^1 = H ; b R^1 = OH ; c R^1 = NH_2

LIV a R^1 = alkyl ; b R^1 = SH

*Here and subsequently, the structures of substituents R in the formulas are the same as in starting thiophenes I.

An easy route to thieno[2,3-d]pyrimidones on the basis of Ib, c has been particularly intensively developed. Thieno[2,3-d]-4-pyrimidones LVa are obtained from amines Ib, c and formamide or from amines Ic and formic acid or orthoformates [34, 112-117], whereas LVb is obtained by condensation of N-acylated amides Ic [117-119]. Thienopyrimidone LVb was also obtained from ester Ib and imido esters or other derivatives of carboxylic acid [120, 121]. 2,3-Trimethylene-substituted compounds of the LV type are formed in the condensation of lactams in the presence of PCl_3 [52, 122]. Ethoxy derivative LVc can be obtained from amino ketone Id and ethyl chlorocarbonate under special conditions [123]. The reaction of N-acylated amino esters Ib with hydrazine leads to 3-aminothienopyrimidones LVd [124]. The reaction of amine Ib with dimethylformamide chloride [sic] and amines has been used for the preparation of derivatives of the LVe type [125], which are also formed from thieno[2,3-d]oxazinones LVI and arylamines [126-128]. Unsubstituted LVI can be obtained extremely simply by intramolecular condensation of esters of 2-acetamidothiophene-3-carboxylic acid XVIII in acetic anhydride [129, 131]. 4-Chlorothienopyrimidines, which are formed from LVa, b and phosphorus chlorides give 4-substituted thienopyrimidines LVII as a result of nucleophilic substitution of halogen [132-135]. The reaction of 4-chlorothienopyrimidines with sodium azide or of hydrazines LVII ($Y = NHNH_2$) with formic acid or orthoformates leads to 3,4-condensed thienopyrimidines LVIII [114, 116, 136]. Amides of o-amino carboxylic acids Ic react with urea [112] or with phosgene [123] to give thienopyrimidine-2,4-diones LIXa. Aryl-substituted LIXb were obtained by a two-step synthesis from compounds of the Ib type and isocyanates; the initially formed substituted thienylurea undergoes cyclization in the presence of a base [137, 138]. Thienopyrimidinediones LIXb can also be synthesized as a result of successive treatment of amides Ic with ethyl chlorocarbonate and aniline [123]. Like acylated mustard oils [139], thiourea reacts with aminothiophenes Ib, to give thieno-4-pyrimidone-2-thiones LXa [140]. N-Aryl-substituted compounds of the LXb type are readily formed from amino esters Ib and aryl isothiocyanates [141-144], during which the initially formed 2-thienyl(aryl)thiourea undergoes cyclization in the presence of alkali. Other heterocondensed systems are also accessible on the basis of pyrimidonethiones LX. For example, the reaction of LXa with α-halo ketones gives thiazolo[2,3-b]thieno[2,3-d]pyrimidones LXIa, along with the isomeric thiazolo[3,2-a]thieno[2,3-d]pyrimidones LXIb, [145-147]. The heterocyclic LXIb system is also formed directly from o-amino esters Ib and thiocyanatoacetone [144, 148]. Pseudosaccharin chloride condenses with both ester Ib and amide Ic to give, as a result of a two-step process, thieno[2,3 : 4,5]-pyrimido[1,2-b][1,2]benzoisothiazole derivative LXII [141].

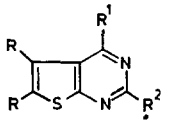


Finally, 2-amino-3-acylthiophenes Id and XXXa can also be used for the construction of 2,3-heterocondensed thiophenes. The Bischler reaction with 2-amino-3-formylthiophene (XXXa) gave thieno[2,3-d]pyrimidines LXIIIa [83, 149]. Thienopyrimidines LXIIIb can also be similarly synthesized from aminothiophene Id [115, 150, 151]. The 3-N-oxides of compounds of the LXIIIb (R^2 = alkyl) type were also prepared by intramolecular condensation of oximes acylated at the amino group – acylthiophene derivatives Id [109, 152].

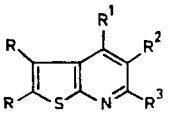
Thieno[2,3-b]pyridines LXIVa can be synthesized from o-amino ketones Id by means of Friedlaender reaction [153]. However, they can also be obtained from aminothiophenes VII and XVII with a free 3 position by means of the Doebner-Miller reaction, as demonstrated for 2-aminothiophene itself (see [154] and the literature cited therein). The synthesis of thieno-4-pyridones LXIVb is based on the reaction of 2-aminothiophene-3-carboxylic acids with ethoxymethylenemalonic ester [155]. 2-Aminothieno[2,3-b]pyridines LXIVc are formed as a result of condensation of 2-amino-3-formylthiophenes XXXa with cyanoacetic acid derivatives [156] (see [157] regarding 1,2-condensed thienopyridines of the LXIVc type).

Thieno[2,3-d]triazin-4-ones LXV are formed by diazotization of o-amino amides Ic [38, 68].

Dihydrothieno[2,3-b]-1,3-diazaborines LXVI were obtained by condensation of amide Ic with phenylboric acid derivatives [5, 158].



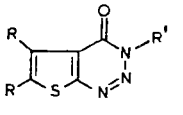
LXIII a, b



LXIV a-c

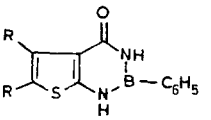
LXIII a R^1 = H, R^2 = alkyl, C_6H_5; b R^1 = aryl, R^2 = OH, alkyl

LXIV a R^1, R^2, R^3 = alkyl, C_6H_5; b R^1 = OH, R^2 = CO_2E, R^3 = H;
c R^1 = H, R^2 = CN, $CO_2C_2H_5$, R^3 = NH_2



LXV

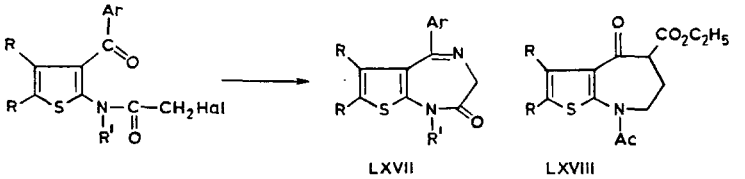
LXV R' = H, CH_3



LXVI

Thieno[2,3-e]-1,4-diazepin-2-ones of the LXVII type, which are potential psychopharmaceutical preparations, are readily obtained from o-amino ketones Id; a good list of studies in this area was compiled in [6]. The usual synthetic method consists in reaction of aminothiophene Id with chloroacetyl chloride or with the bromides of α-bromo carboxylic acids and subsequent ammonolysis [28, 29, 159-162]. However, intermediate replacement of chlorine by iodine is, as a rule, necessary, since otherwise deacetylation occurs under the influence of ammonia [159-161]. In this connection, reductive azidolysis of the chloroacetyl derivative is also used [29, 163, 164]. If hydroxylamine is used in place of ammonia, 4-N-oxides of compounds of the LVII type are obtained [29]. Thienodiazepinones LVII were also synthesized from the phthalimidoacetyl derivatives of aminothiophene Id [29, 165, 166] or as a result of direct cyclization of aminothiophene Id by means of benzyloxycarbonylaminoacetyl chloride [28] or oxazoline-2,5-dione [167, 168] (direct condensation of Id with glycine ester has also been mentioned [163, 164]). Enamine XIV, which initially undergoes cyclization to give the imine of 2-amino-3-thienyl phenyl ketone [48], also condenses with glycine ester hydrochloride to give thienodiazepine LVII [R' = H, RR = $(CH_2)_4$, Ar = C_6H_5]. Secondary reactions have also been described for thienodiazepinones LXVII: for example, see [169-171] for the preparation of 2,3-triazolothienodiazepinones, [172] for the nitration of compounds of the LXVII type with a free α position, and [173, 174] for reactions involving the diazepine ring.

Tetrahydrothieno[2,3-b]azepinone LXVIII was synthesized by Dieckmann condensation from o-amino ester Ib, which is initially successively N-acetylated and N-alkylated by α-bromopropionic acid ester [32].



LXVII LXVIII

LXVII R' = H, alkyl, aryl, acyl; Ar = phenyl, substituted phenyl, pyridyl

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