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SYNTHESIS OF HIGHER ALICYCLIC COMPOUNDS FROM THIOPHENE DERIVATIVES

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Abstract—A new method is proposed for the synthesis of higher alicyclic compounds in which bi- and tricyclic molecules possessing the thiophene ring are desulphurized with the aid of Raney nickel New routes to many-membered bi- and tricyclic compounds possessing the thiophene ring have been developed, based on acyloin condensation and intramolecular acylation and alkylation.

MACROCYCLIC chemistry is undergoing a period of intensive growth. The past 10–15 years have seen the development of new methods for the synthesis of macrocycles,* the elucidation of physical and chemical properties of the simpler representatives of this class and an ever increasing study of the more complex, naturally-occurring compounds possessing large and medium cycles as structural elements.

The study of macrocyclic compounds contributes to the advance of organic chemical theory, in particular the influence of steric factors on physical properties and chemical behaviour. Owing to puckering peculiar to many-membered rings (of medium size) oppositely situated non-bonded substituents can be brought in close enough to bring about interaction (transannular effect). Investigations on macrocyclic compounds have considerably broadened our concepts of ring strain and brought out many interesting correlations between this property and the reactivity of rings. X-ray, infrared, ultraviolet data and dipole moment measurements have yielded much valuable information on the mutual arrangement of the atoms in many-membered rings and will lead to further progress in conformational analysis (for a more detailed discussion see reviews[1–3]). An interesting development is the synthesis of the "catenane" system,[4] in which two macrocycles are interlocked like the links of a chain. Studies in this field using elements of topolgy[5] predict new isomers for large rings. These studies will no doubt lead to reconsideration of our concept of a molecule, inasmuch as in a catenane the two rings are held together not by a chemical bond, but "mechanically" so that it is as yet undecided whether the system is to be regarded as a single molecule or as two separate ones.

The importance of macrocyclic compounds became apparent in studies of natural products. Until recently physiologically active macrocycles included only a few

* We do not discriminate between the terms "macrocycle" and "many-membered cycle" embracing under this concept both medium (eight- to twelve-membered) and large (thirteen- and more membered) rings.

[1] Ya. L. Gol'dfarb and L. I. Belen'kii, *Uspekhi Khim.* **26,** 362 (1957).
[2] Ya. L. Gol'dfarb and L. I. Belen'kii, *Uspekhi Khim.* **29,** 470 (1960).
[3] J. Sicher in *Progress in Stereochemistry* Vol. 3; pp. 202–263, London (1962).
[4] E. Wassermann, *J. Amer. Chem. Soc.* **82,** 4433 (1960).
[5] H. L. Frisch and E. Wassermann, *J. Amer. Chem. Soc.* **83,** 3789 (1961).

alkaloids, some odoriferous principles and the porphyrins. Now the number of macrocyclic compounds possessing strongly expressed physiological and in particular, antibiotic activity has increased greatly (Refs. 6–11). This suggests that the macrocycle may not be fortuitous in such molecules, but is of fundamental importance in the manifestation of bilogical activity; in that these may be a correspondence in structure with that of the biological receptor. Several papers have appeared recently on the synthesis of physiologically active macrocycles (Refs. 12–14).

The importance of developing methods for the synthesis of macrocyclic systems is, therefore, abundantly clear. Most synthetic routes hitherto followed are based on the cyclization of long chain bifunctional compounds, often not readily available. The yields vary greatly, depending upon the number of members in the ring and the method of cyclization, but in all cases ring structure is predetermined by the structure of the open chain. However it is difficult and often practically impossible subsequently to incorporate a substituent into the ring (see review[15]).

The Carothers depolymerization method (Ref. 15) is of considerable preparative interest. Its application however, is limited to heterocyclic compounds (primarily lactones) where depolymerization is reversible and high yields can be obtained by removal of the products from the reaction zone. The classic Ruzicka pyrolysis of dicarboxylic acid salts to yield higher alicyclic ketones which essentially amounts to degradation of the polymeric salt gives low yields and it is at present no longer of practical interest (Ref. 15).

Latterly a variety of methods for the synthesis of macrocyclic compounds have been developed, based on the use of the so-called "auxiliary bond" ("Hilfsbindung", Ref. 15). In this case the marocycle is formed via a bi- or polycyclic system of three- to seven (more often five- to six) membered rings. Cyclization of long chains is thereby avoided which eliminates the necessity of high dilution. Well known examples of such syntheses are (Ref. 15) the Willstätter preparation of cycloöctatetraene and cycloöcta-1,5-diene from pseudopelletierine or the Kriege cyclodecan-6-ol-1-one synthesis from decalin hydroperoxide. It has recently been shown that the Reppe synthesis of cycloöctatetraene[16] and the Wilke synthesis of cyclodoeca-1,5,9-triene[17,18] also belong to the auxiliary bond type of syntheses, the role of the auxiliary bond being played by co-ordination bonds.

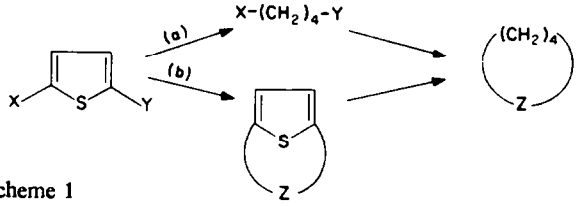
[6] M. M. Shemyakin, A. S. Khokhlov, M. N. Kolosov, L. D. Bergel'son and V. K. Antonov, *Khimiya Antibiotikov* (3rd. Edition) pp. 601–612, 1057–1172, USSR, Acad, of Sciences, Moscow (1961).
[7] A. R. Battersby and H. F. Hodson, *Quart. Rev.* **14,** 77 (1960).
[8] R. Adams and M. Gianturco, *Angew. Chem.* **69,** 5 (1957).
[9] V. du Vigneaud, C. Ressler, J. W. Swan, C. W. Roberts and P. G. Katsoyannis, *J. Amer. Chem, Soc.* **76,** 3115 (1954).
[10] R. B. Woodward, *Angew. Chem.* **72,** 651 (1960).
[11] T. G. Halsall and D. W. Theobald, *Quart. Rev.* **16,** 101 (1962).
[12] A. Luttringhaus, L. Kerp and H. Preugschas, *Arzneimittel-Forsch.* **7,** 222 (1957).
[13] K. Stach and W. Winter, *Arzneimittel-Forsch.* **12,** 194 (1962).
[14] R. A. Maxwell, R. P. Mull and A. J. Plumer, *Experientia* **25,** 267 (1959).
[15] K. Ziegler in Houben-Weyl, *Methoden der Organischen Chemie* Bd. 4/2, S.729–822. Verl. Georg. Thieme, Stuttgart (1955).
[16] G. N. Schrauzer and E. Eichler, *Chem. Ber.* **95,** 550 (1962).
[17] G. Wilke, M. Kröner and B. Bogdanovic, *Angew. Chem.* **73,** 755 (1961).
[18] G. Wilke and M. Kröner, *Angew. Chem.* **71,** 574 (1959).

Finally a number of new methods for the preparation of substituted cycloöctatetraenes and cycloöctatrienes based on the valence isomerization of the systems bicyclo-(4,2,0)-octa-2,4,7-triene, bicyclo(4,2,0)-octa-2,4-diene and cis-1,2-divinylcyclobutane to the corresponding 8-membered rings,[19–23] may be classified among syntheses of this type.

The routes to higher cyclic compounds which have been developed are based on the reductive desulphurization of thiophene derivatives with the aid Raney nickel. There are two way in which thiophene can be used for this purpose:

1. Long-chain bifunctional aliphatic compounds[24–25] are prepared by reductive desulphurization and these are subjected to ring closure by one of the usual methods. It should be noted that the thiophene ring greatly facilitates incorporation of various substituents in the molecule.

2. Bi- or polycyclic compounds possessing the thiophene ring are first synthesized and then the sulphur atom serving as a bridge is removed.



Scheme 1

This second novel method* is the more advantageous in that in addition to the bicyclic thiophene derivatives obtained as intermediates, which are themselves of interest, should in general give higher yields of the many-membered monocyclic compounds than the first method when using the same chemical reactions for ring closure. According to the literature (see survey in Ref. 15) cyclization should be facilitated by the presence of a "rigid grouping" (in this case the thiophene ring). Furthermore, the thiophene ring can be utilized not only for lengthening the carbon chain and incorporation of substituents; but, of particular significance, due to its aromatic character, it can play the part of the second function eliminating the necessity of incorporation of the latter.

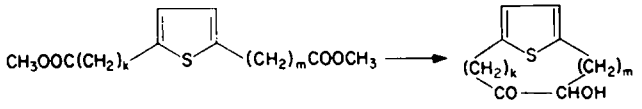
One of the best methods for the formation of large and medium sized rings is the acyloin condensation of dicarboxylic acid esters by the method proposed by Hansley,[26] and elaborated by Prelog[27] and Stoll.[28] The reaction is carried out under

* Essentially this method is close to the syntheses of the "auxiliary bond" type. However, a fundamental difference is that the intermediate bi- or polycyclic compounds of the former method already contain the preformed many-membered ring as one of its structural elements. Although this itself does not necessarily place the method above the others, its additional synthetic possibilities make it very valuable from a preparative standpoint.

[19] K. Alder, H. A. Dortman, *Chem. Ber.* **87**, 1492 (1954).
[20] E. Vogel, O. Roos and K. H. Disch, *Liebigs Ann.* **653**, 55 (1962).
[21] D. Bryce-Smith and J. E. Lodge, *Proc. Chem. Soc.* 333 (1961).
[22] E. Govenstein and D. V. Rao, *Tetrahedron Letters* No. 4, 148 (1961).
[23] E. Vogel, K. H. Ott and K. Gajek, *Liebigs Ann.* **644**, 172 (1961).
[24] Ya. L. Gol'dfarb and M. L. Kirmalova, *Izvest. Akad. Nauk. Otd. Khim. Nauk*, 570 (1955).
[25] N. P. Buu-Hoi, M. Sy and N. Dat-Xuong, *C.R. Acad. Sci., Paris* **240**, 442 (1955).
[26] V. L. Hansley, U.S.Pat. 2 228 268; *Chem. Alstr.* **35**, 2534 (1941).
[27] V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).
[28] M. Stoll and J. Hulstkamp, *Helv. Chim. Acta* **30**, 1815 (1947).

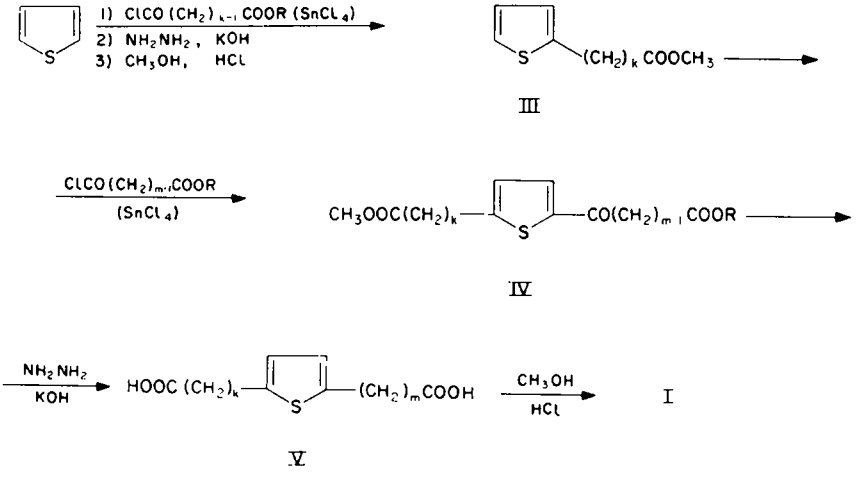
heterogeneous conditions, using finely dispersed molten sodium in boiling xylene in a pure nitrogen atmosphere. As a rule the yields are very good. Characteristic of this reaction is its high rate, the surface area of the metallic sodium playing a decisive role. Dispersion of the molten metal is achieved by means of high speed stirrers operating at about 10000 rev/min. The part played by the heterogeneity of the medium in the macro-ring formation will be discussed presently; here in passing, it will only noted that the highly dispersed sodium makes rapid cyclization of the dicarboxylic acid esters possible without high dilution techniques.

Starting from ester of type I, it was natural to attempt[29] the acyloin cyclization for the preparation of thiophene-possessing bicyclic compounds.



Scheme 2a I II

According to the literature,[30-32] p,p'-disubstituted benzenes readily give high yields of the corresponding acyloins provided ring closure is sterically possible. Synthesis of the initial esters was carried out according to the scheme:



Constants and yields of diesters I as well as of the intermediates in their synthesis are summarized in Table 1.

The ordinary conditions for the acyloin condensation were found to be unsuitable for the cyclization of esters of the thiophene series,* This can be explained on the one hand by the degradative action of sodium on the thiophene ring under the reaction

* Similar findings were recently published by American workers[33] who were unable to carry out the acyloin condensation of dicarboxylic esters of the thiophene series.

[29] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, *Izvest. Acad. Nauk SSSR, Otdel. Khim. Nauk* No. 10, 1262 (1957).

[30] K. Wiesner, D. Macdonald, R. Ingraham and R. Kelly, *Canad. J. Res.* **28**, 561 (1950).

[31] D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.* **73**, 5691 (1951).

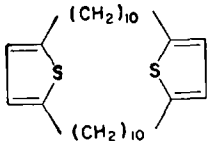
[32] D. J. Cram and H. Daeniker, *J. Amer. Chem. Soc.* **76**, 2743 (1954).

[33] R. O. Schuetz and R. A. Baldwin, *J. Org. Chem.* **27**, 2841 (1962).

conditions and on the other, by the deactivation of sodium by the sulphur-containing degradation products. Lowering the reaction temperature to 50–60° did yield the desired acyloin [10]-α-cyclothien-6-ol-5-one* (II), k = m = 4) but in only 30% yield based on the ester, the latter being converted to the extent of 15%. The low conversion can be explained by the fact that this temperature sodium is in the solid state so that its surface is not refreshed on deactivation. Somewhat higher yields of the acyloin were obtained with a new condensation reagent, namely sodium-potassium alloy, which is liquid at ordinary temperatures. But even in this case, conversion of ester I (k = m = 4 and k = 4, m = 5) did not exceed the 25%.

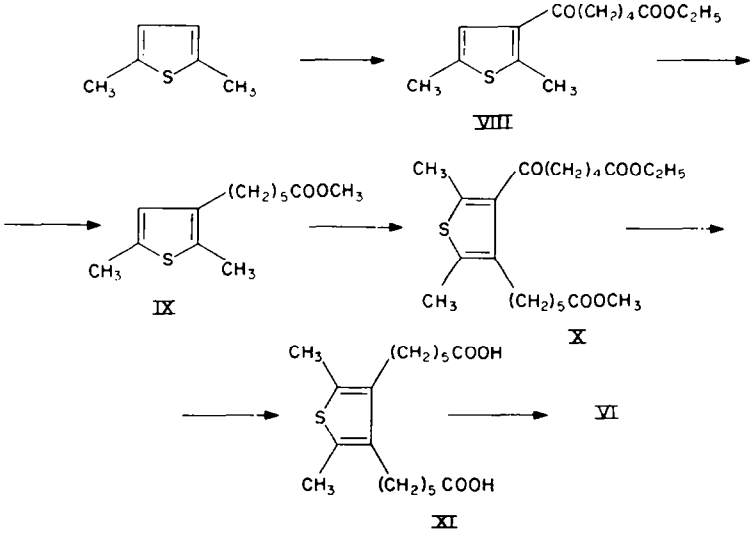
An important development is that ring closure of ester molecules with the aliphatic chains bonded to the thiophene ring in the β-position, namely 2,5-dimethyl-3,4-bis-(5-methoxycarbonylamyl)thiophene (VI)† in the presence of the K–Na alloy proceeds

* The authors have proposed[34] the name cyclothienes for bridged systems possessing thiophene rings. Bracketed figures before the name denote the number of atoms in the bridge backbone; this is followed by the letter α or β showing the position of linkage to the thiophene rings. Finally, the name shows also the number of thiophene rings. Thus the compound



is [10,10]-α-cyclodithiene. All atoms are numbered along the perimeter beginning with the end atom of the longest chain adjacent to the least substituted thiophene ring. Substituents are designated in the usual manner. For instance the name of II (k=m=4) is [10]-α-cyclothien-6-ol-5-one.

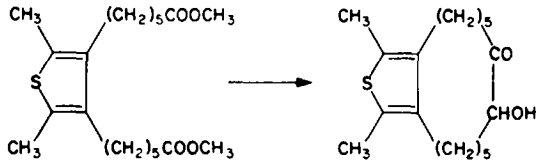
† The ester VI was synthesized according to the Scheme:



Constants and yields of the products VI, VIII-XI are given in Table 1.

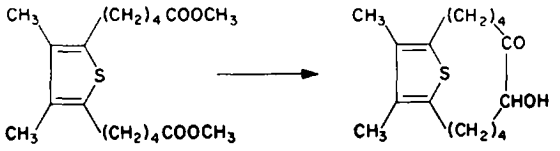
[34] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, *Zh. Obshchei Khim.* **29**, 3564 (1959).

with 100% conversion and gives the acyloin VII in 70% yield.



Scheme 2b VI VII

From 3,4-dimethyl-2,5-bis-(4-methoxycarbonylbutyl)thiophene (XII)* the corresponding acyloin (XIII) was prepared in 40% yield with 100% conversion.

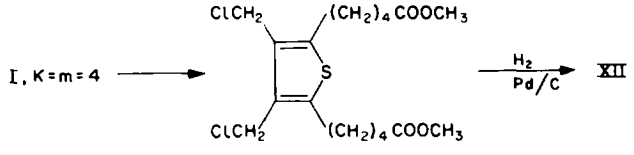


Scheme 2c XII XIII

TABLE 1. INTERMEDIATES IN THE SYNTHESIS OF CYCLIC ACYLOINS POSSESSING THIOPHENE RINGS

Compound	B.p. °C (mm)	M.p. °C	n_D^{20}	d_4^{20}	Yield of last stage, %
III, k = 4	141·5–143 (14)	—	1·5067	1·0894	98
III, k = 5	113–114 (1)	—	1·5032	—	76
IV, m = k = 4, R = CH_3	—	67·5–69	—	—	72·5
IV, m = 5, k = 4, R = C_2H_5	224–225 (0·5)	—	1·5158	1·1292	71·5
IV, m = k = 5, R = C_2H_5	233–237 (1)	33–34·5	—	—	77·5
V, m = k = 4	—	140·5–142·5	—	—	97
V, m = 5, k = 4	—	80·5–83·8	—	—	92
V, m = k = 5	—	60–68	—	—	89
I, m = k = 4	182–185 (2)	—	1·5000	1·0936	87·5
I, m = 5, k = 4	194–195·5 (1)	—	1·4986	1·0872	74
VIII	155·5–156·5 (0·5)	—	1·5154	1·1143	84
IX	120–121 (1)	—	1·5028	1·0873	89
X	203–214 (1)	—	1·5079	1·0908	82
XI	—	93–93·7	—	—	95·5
VI	200–205 (1)	—	1·5018	1·0669	76·5
XIV	—	63·8–64·2	—	—	56·5
XII	177–179 (0·25)	—	1·5075	1·0844	43

* Synthesis of the ester XII was carried out according to the Scheme:



XIV

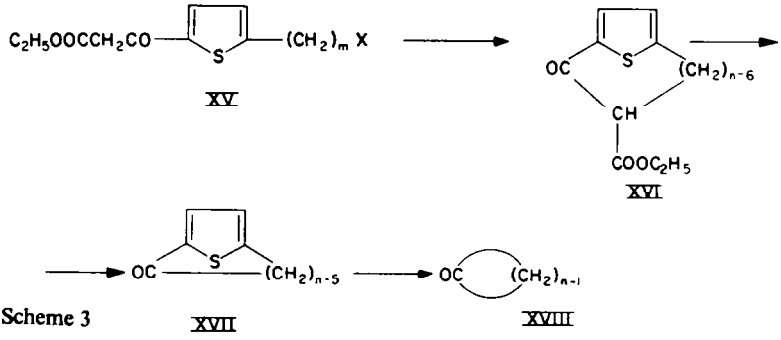
for constants and yields of XII and XIV see Table 1.

After performing a number of acyloin condensations (K—Na alloy induced) it was concluded (see Table 2) that completely substituted thiophenes with no hydrogen in the ring undergo ring closure more readily than their non-substituted analogues.*

TABLE 2. CONSTANTS AND YIELDS OF THIOPHENE RING POSSESSING CYCLIC ACYLOINS (II, VII, XIII)

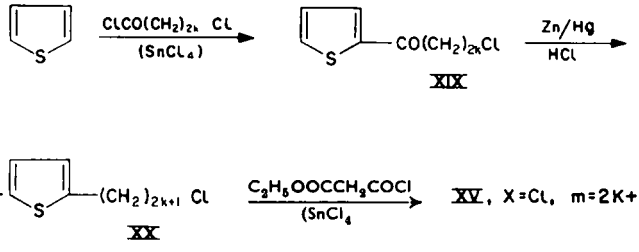
Initial ester	Product	Conversion of ester (%)	Yield of acylion based on ester consumed	M.p. of acyloin °C	B.p. of acyloin °C (mm)
I, k = m = 4	II	25·4	40·7	69·5–71	169–178 (1)
I, k = 4, m = 5	II	26·5	39·2	62–64	167–169 (0·3)
VI	VII	100	72·0	105·5–107	—
XII	XIII	100	42·5	117–119	—

As the acyloin condensation as a method for the synthesis of bicyclic systems possessing the thiophene ring has a number of serious limitations, other methods to build the many-membered thiophene-possessing system and also of its reductive desulphurization were investigated. One route[36,37] developed is intramolecular alkylation of ω-halo-β-ketoesters of the type XV, with subsequent ketonic cleavage and reductive desulphurization:



Scheme 3

For preparation of starting materials use was made of thiophene, chloroalkanoic



* A paper on the acyloin condensation has been published by the authors in the Izvestia of Academy of Sciences.[35]

[35] S. Z. Taits and Ya. L. Gol'dfarb, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, No. 7, 1289 (1963)

[36] S. Z. Taits and Ya. L. Gol'dfarb, *Izvest. Acad. Nauk SSSR, Otdel Khim. Nauk*, 1698 (1960) Author's Certificate, USSR, N 132221.

[37] Ya. L. Gol'dfarb, S. Z. Taits and V. N. Bulgakova, *Izvest. Akad. Nauk, Otdel Khim. Nauk*, No. 7, 1299 (1963).

acids (obtained from the products of ethylene and carbon tetrachloride telomerization) and monoethyl malonic ester chloride (its synthesis often described as difficult gives yields as high as 70% by a modification of the preparative method).

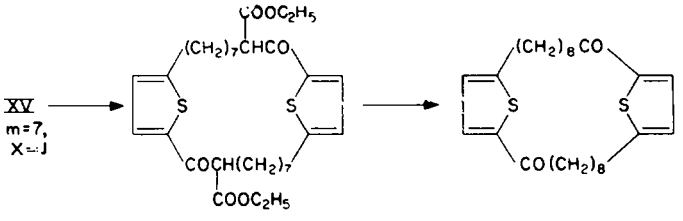
According to this reaction scheme* the keto esters (XV) were obtained in high yield and cyclized in methyl ethyl ketone over finely ground potassium carbonate according to Hunsdieker[38] for aliphatic ω-halo-β-ketoesters. Yields of 80% were obtained in the case of XVI (n = 15 and 17) which on ketonic cleavage followed by reductive desulphurization were transformed into exalton and dihydrocivetone respectively, these compounds being obtained in very satisfactory yields and by a simpler method than that described in the literature (see, for instance Ref. 39).

TABLE 3. INTERMEDIATES IN THE SYNTHESIS OF CYCLIC β-KETOSTERS WITH A THIOPHENE RING

K	ω-Chloroalkyl(thienyl-2)ketones (XIX)				2-(ω-Chloroalkyl)thiophenes (XX)			
	B.p. °C/mm	M.p. °C	Yield %	M.p. of semicarbazone	B.p. °C/mm	n_D^{20}	d_4^{20}	Yield %
2	110–116/0·1	38–39	92·5	148–149	85–86/0·05	1·5250	1·1012	64·5
3	132–134/0·3	28–30	89·0	123–124	94–96/0·07	1·5150	1·0542	67·5
4	167–169·5/1·5	23–25	78·0	101·5–102·5	126·5–131/0·7	1·5080	1·0271	66·0
5	193–197/1·0	39–40	78·5	108·5–109·5	116–124/0·04	1·5050	1·0012	50·0

K	2-(ω-Chloroalkyl)-5-(ethoxycarbonylacetyl)-thiophenes (XV, X = Cl, m = 2k + 1)			2-(ω-Iodoalkyl)-5-(ethoxycarbonylacetyl)-thiophenes (XV, X = J, m = 2K + 1)			
	B.p. °C/mm	M.p. °C	Yield	M.p. °C	B.p. °C/mm	n_D^{20}	Yield, %
2	176–177/0·25	45·5–46·5	42·0	—8	—	1·5700	82·5
3	140–150/4·10⁻⁵	—	69·5	—	150/2·5 . 10⁻³	1·5614	97·3
4	—	30·6–31·3	71·5	29·5–30·7	—	—	100
5	—	38·2–38·7	59·0	41·5–42·5	—	—	91·5

From 2-(7-iodoheptyl)-5-(ethoxycarbonylacetyl)thiophene (XV, m = 7, X = J) the only product isolated (yield 47%) was 2,15-di-ethoxycarbonyl-[9,9]-cyclodithiene-1, 14-dione (XXI) resulting from interaction of two molecules of the initial compound. On ketonic cleavage it was transformed into [9,9[-α-cyclodithiene-1,14-dione (XXII, m = 8) identical with the diketone formed on cyclization of 9-(thienyl-2)pelargonyl chloride (see below):



XXI XXII, m=8

* Constants and yields of ω-halo-β-ketoesters of type XV, and of their intermediates, as well as of some derivatives, are given in Table 3.

[38] H. Hunsdieker, *Chem Ber.* **75**, 1196, 1200 (1942); **76**, 142 (1943).

[39] S. Bhattacharrya and H. Mathur, *Chem. & Ind.* 1087 (1960).

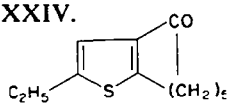
2-(5-Iodoamyl)-5(ethoxycarbonyl acetyl)thiophene (XV, X = J, m = 5) under conditions of the reaction formed only a high molecular product. The properties and yields of the cyclization products obtained according to the aforementioned scheme are summarized in Table 4.

TABLE 4. CYCLIZATION PRODUCTS OF 2-(ω-IODOALKYL)-5-(ETHOXYCARBONYL ACETYL) THIOPHENES

Initial compound XV, m =	Name	Cyclization product		
		M.p. °C	B.p. °C/mm	Yield, %
5	—	—	—	—
7	2,15-Diethoxycarbonyl-[9.9]-α-cyclodithien-1,14-dione (XXI)	132·5–134	—	47·5
9	2-Ethoxycarbonyl-[11]-α-cyclothien-1-one (XVI), n = 15)	—	189–192/0·15	67·0
11	2-Etoxycarbonyl-[13]-α-cyclothien-1-one (XVI, n = 17)	—	160/5 . 10^{-3} (bath temp)	84·0

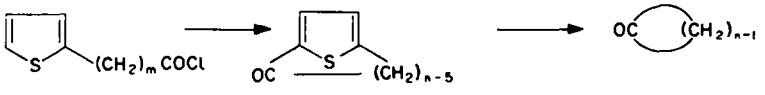
The third route to macrocyclic compounds developed is the intramolecular acylation of ω-(thienyl-2)alkanoyl cholrides (XXIII) with subsequent conversion of the cyclization products into alicyclic ketones by means of Raney nickel desulphurization.[29,34]

When this work was started cyclization of only the lower acid chlorides of this series, namely 4-(thienyl-2)butyryl chloride,[40] 5-(thienyl-2)valeryl chloride and its α′-alkyl-substituted derivatives[41] has been described in the literature. Somewhat later a report appeared[42] on the cyclization of 6-(5-ethylthienyl-2)caproyl chloride to the eight-membered cyclic ketone XXIV.



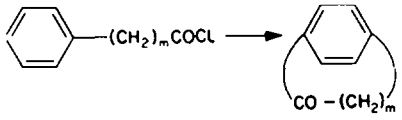
XXIV

One may assume that with longer aliphatic chains in ω-(thienyl-2)alkanoic acids the reaction should be directed to the more active α′-position,* according to scheme 4a:



Scheme 4a XXIII XVII XVIII

* Huisgen *et al* have shown the ω-phenylalkanoyl chlorides, beginning with m = 8, in the presence of aluminium chloride[43] or aluminium bromide[44] under high dilution conditions yield *para*-cyclization products (XXV).



XXV

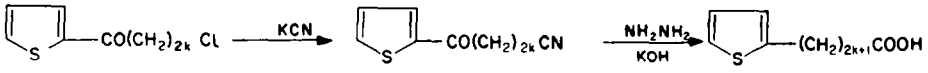
[40] L. Fieser and M. Kennelly, *J. Amer. Chem. Soc.* **57**, 1611 (1935).
[41] P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr*, 680 (1955).
[42] P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 1152 (1956).
[43] R. Huisgen, W. Rapp, J. Ugi, H. Walz and J. Glogger, *Liebigs Ann.* **586**, 52 (1954).
[44] R. Huisgen and J. Ugi, *Chem. Ber.* **93**, 2693 (1960).

This route is especially attractive, not requiring bifunctionality of the thiophene compound (the role of second function being played by the unsubstituted α'-position of the thiophene ring) which makes it easier to prepare the initial compounds. In other words with this procedure one can fully make use of the merits of the thiophene-based synthesis of mactocycles.

We have studied in detail the various conditions under which the reaction is carried out (solvent, condensing agent, temperature, reaction time, dilution).[34,45] As a rusult it was found that ω-(thienyl-2)alkanoyl chlorides undergo ring closure satisfactorily on using high dilution technique with carbon disulphide or chloroform as solvent and partially hydrolysed (by one mole of water) aluminium chloride etherate as the condensing agent,[45a,c,d] Under such conditions the bicyclic ketones XVII (n = 14–17) are obtained in yields which can be regarded as fairly high for such systems (53–63%). Reductive desulphurization with Raney nickel gave higher alicyclic ketones (XVIII), musk like cyclotetradecanone, cyclopentadecanone (exaltone) cyclohexadecanone and cycloheptadecanone (dihydrocivetone) in yields of 75–90%.

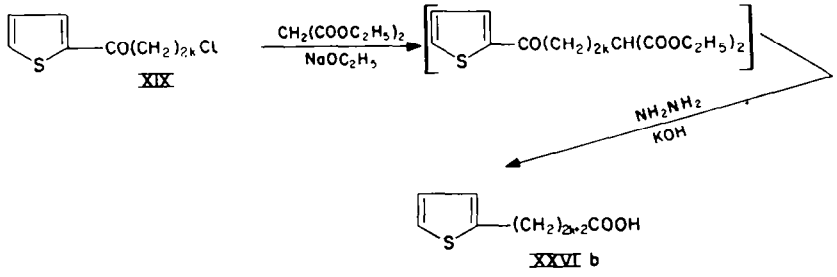
The authors have also developed a method for the preparation of ω-(thienyl-2) alkanoic acids (XXVI)[45c,46] from the available ω-chloroalkanoic acids via ω-chloro alkyl(thienyl-2)ketones according to the scheme:

(a) For acids with even number of carbon atoms in the aliphatic chain:*



XIX XXVII XXVI a

(b) For acids with odd numbers of carbon atoms in the aliphatic chain:



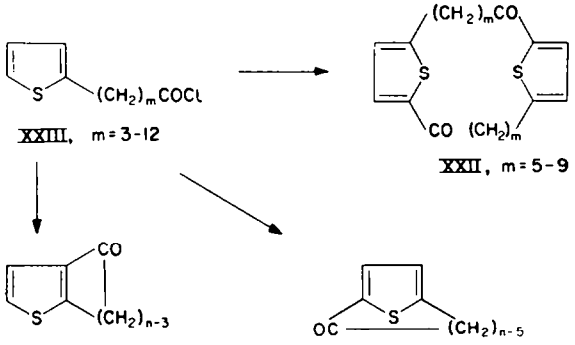
XIX XXVI b

Hence a method is now available for the preparation of higher alicyclic ketones from thiophene and ω-chloroalkanoic acids.

* In the synthesis of ω-(thienyl-2)alkanoic acids the authors have isolated the intermediate ω-cyanoalkyl-(thienyl-2)ketones (XXVII): k = 3, m.p. 50, 5–52·5°, yield 79%, k = 4, m.p. 53–54·5°, yield 98·5% and k = 5, m.p. 63–64°, yield 93·5%.

[45a] L. I. Belen'kii, S. Z. Taits and Ya. L. Gol'dfarb, *Dokl. Akad. Nauk SSSR* **139**, 1356 (1961).
[b] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, Author's Certificate 120841;
[c] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, Author's Certificate 140432;
[d] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, Authors, Certificate 140433.
[46] L. I. Belen'kii, S. Z. Taits and Ya. L. Gol'dfarb, *Izv. Acad. Nauk SSSR, Otdel Khim. Nauk* 1706 (1961).

9-Thienyl-2-pelargonyl chloride (XXIII, m = 8) undergoes ring closure to [9]-α-cyclothien-1-one (XVII, n = 13) only to the extent of 8% under the conditions developed. From the cyclization products of 7-(thienyl-2)enanthyl and 8-(thienyl-2) caprylyl chlorides (XXIII, m = 6 and 7) no monoketones could be isolated, only intermolecular cyclization products of the type of α-cyclodithienediones (XXII) being obtained. The diketones XXII are also formed together with monoketones in the case of 6-(thienyl-2)capronyl, 9-(thienyl-2)-pelargonyl and 10-(thienyl-2)-capryl chlorides (see Scheme 4b). By selection of suitable conditions, the yields of the monoketones (XVII or XXVIII) can be increased and at the same time the yields of the diketones XXII and of the polycondensation products useless in this study decreased. Consequently, under acylation conditions acid chlorides of type XXIII are transformed into three types of compounds (monoketones, diketones and polycondensation products). Predominate formation of one of these types can be achieved by suitable selection of the reaction conditions. A decisive factor for the intramolecular course of the reaction is a sufficiently low stationary concentration of the substance undergoing cyclization (Ref. 15).



Scheme 4b

The data presented are in good agreement with that reported by Huisgen *et al.* on the cyclization of ω-phenylakanoyl chloride,[43] except that the yields of the ketones XVII (n = 14–17) were about twice those given by Huisgen for their benzene analogues (XXV), though the reactions were carried out at greater dilutions than those used by Huisgen. The higher yields are no doubt due to the greater reactivity of the thiophene ring leading to a lower stationary concentration of the chloride (XXIII).*

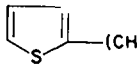
6-(Thienyl-2)caproyl chloride (XXIII, m = 5) forms a β-acylation product thiophenocycloöctanone (XXVIII, n = 8) in a yield of about 9% while Huisgen *et al.* obtained benzocycloöctanone by cyclization of 6-phenylcaproyl chloride in 77% yield. This difference in yields of similar condensed systems of the benzene and thiophene series is explained by the strongly manifested nonequivalence of the α- and β-positions of the thiophene ring, whereas the *o*- and *p*-positions of the benzene ring have approximately the same reactivities. The existence of a free α′-position in the acid chloride XXIII (m = 5) leads to marked intermolecular cyclization with the

* The higher yields of the cyclization products could be due not only to the relatively higher reactivity of the thiophene than the benzene ring but also a higher activity of the condensing agent (cf.[44]). However, the one used in this study is less active than anhydrous aluminium chloride. For instance it did not catalyse the intramolecular acylation of 10-phenylcapryl chloride.

formation of [6,6]-α-cyclodithiene-1,11-dione (XXII, m = 5).* If the α'-position is occupied as in the case of 6-(5-ethylthienyl-2)caproyl chloride, the corresponding monoketone with an eight-membered ring (XXIV) is formed, the yield under conditions of the experiment being about 50%. When such compounds as 4-(thienyl-2) butyryl and 5-(thienyl-2) valeryl chlorides (XXIII, m = 3 and 4) leading to a 6- or 7-membered ring are cyclized, the ketones XXVIII (n = 6 and 7) are formed in high yields and no other products are detected. The cyclization is carried out in benzene in the presence of tin chloride, without the use of high dilution technique.

The constants and yields of ω-(thienyl-2)alkanoic acids and their chlorides are given in Table 5. Data on the cyclization products of ω-(thienyl-2) alkanoyl chlorides[47] are summarized in Table 6.

A study of the intramolecular acylation of ω-(thienyl-2)alkanoyl chlorides revealed that heterogeneity of the medium plays an important role in the cyclization reaction.[48]

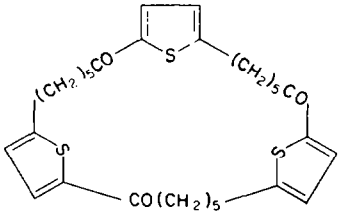
TABLE 5. ω-(THIENYL-2)ALKANOIC ACIDS 

XXVI

m	M.p. °C	B.p. °C (mm)	Method of preparation[a]	Yields	Acid chlorides	
					B.p. °C (mm)	Yield
3	—	172–174/20	A	54	114–116/6	90·5
4	39–41	163–164/9	A	69	102–105/1	76·5
5	41–41·5	—	A	62	118–119/3·5	84·0
6	28–30	148–152/0·2	B	67	120–125/0·5	79·0
7	14·2–15·6	147–150/0·03	B	58	157–160/3	55·0
8	35·3–36	—	A	66·5	142–146/1	87·0
9	33–33·8	171–173/1	A	59	163–165/2	92·0
			B	68		
10	47–48·5	165–170/0·05	B	45·5	154–155/0·2	91·0
11	39–40·5	200–205/0·1	B	68	175–180/0·7	76·0
12	57·5–59	—	B	39	decomposes on distillation at 0·2 mm	

[a] Method A: based on thiophene and the acid esters of dicarboxylic acids.
Method B: based on thiophene and ω-chloroalkanoic acids.

* The authors were also able to isolate products of the intermolecular cyclization of three 6-(thienyl-2)caproyl chloride molecules namely [6.6.6]-α-cyclotrithiene-1,11,-21-trione,



m.p. 89–90·5°, λ_{max} 226 mμ (ε 24100) and λ_{max} 294 mμ (ε 34659).

[47] Ya. L. Gol'dfarb, S. Z. Taits and L. I. Belen'kii, *Izvest. Akad. Nauk, Otd. Khim. Nauk* N 8, (1963).

[48] S. Z. Taits, L. S. Belen'kii and Ya. L. Gol'dfarb, *Izvest. Akad. Nauk SSSR, Otdel Khim. Nauk*, N 8, 1460 (1963).

TABLE 6. CYCLIZATION PRODUCTS OF ω-(THIENYL-2)ALKANOIC ACIDS*

Initial acid chloride, m	Products	Yield	B.p. °C(mm)	M.p. °C	λ_{max} mμ	ε_{max}	λ_{max} mμ	ε_{max}	Semicarbazones		
									M.p. °C	λ_{max}[a] mμ	ε_{max}
3	XXVIII, n = 6	92·0	81–84/0·3	34·3–35·5	220[a]	15000	251	12600	210·5–212	274	24400
4	XXVIII, n = 7	88·0	114·5–115·5/3	—	219[a]	12400	252	10800	187–188	274	21600
5	XXVIII, n = 8	9·4	100–150/1·1	45·7–47·3	218[a]	9800	255	9200	213–215	274	24400
	XXII, m = 5	2·0†	180–200·5 . 10^{-5}	141–143	266[a]	15000	295	21500	—	—	—
6	XXII, m = 6	4·6	120–180/5 . 10^{-3}	107·8–109·3	268[a]	16800	296	24200	—	—	—
7	XXII, m = 7	12·8	150–200/5 . 10^{-5}	97 98	266[a]	17000	296	24400	—	—	—
8	XVII, n = 13	8·3	—	—	—	—	—	—	191·5–193·5	292	15200
	XXII, m = 8	4·0†	150–200/1 . 10^{-5}	81 –83	267[a]	17195	294	24620	—	—	—
9	XVII, n = 14	54·5	149–152/1	40–41	265[b]	5400	285	10000	188·5–189·5	302	19600
					270[a]	5700	297	12000	—	—	—
	XXII, m = 9	12·0†	180–200/5 . 10^{-5}	102–104	266[a]	17000	295	24000	—	—	—
10	XVII, n = 15	63·5	128–132/0·05	44·5–46·5	266[b]	6995	286	10950	194–196	302	17200
11	XVII, n = 16	62·5	162–165/0·5	31 ·32	266[b]	8660	288	12000	214–215	305	16600
12	XVII, n = 17	60·0	157/0·005	—	266[b]	7020	288	10000	255–226·5	308	18200

Solvents: *a* – alcohol, *b* = n = heptane

* Cyclization of the acid chlorides XXIII, m = 3 and 4 was carried out in benzene in the presense of tin chloride. In all other cases it was carried out in chloroform in the presence of the partial hydrolysis products of $AlCl_3$ etherate, using high dilution technique.

† The yield of diketones can be augmented to 25–30% on changing the reaction conditions, but then the yield of monoketones is considerably diminished and in some cases no monoketone can be isolated at all.

It was found that satisfactory yields of macrocyclic ketones of the type XVII can be obtained by using a condensing agent with a sufficiently developed surface. (The data have been included in Table 6.) While the solid phase formed in the partial hydrolysis of aluminium chloride etherate (which from analytical data is a mixture of aluminium oxychlorides) does not catalyse the acylation, the chloroform soluble fraction (which is mainly unchanged $AlCl_3$ etherate) on being separated from the solid phase, can still serve as condensing agent, but only gives about $\frac{1}{3}$ of the yield than when in combination with the "inactive" solid phase. Quite satisfactory yields can be obtained by using $AlCl_3$ etherate in the presence of anhydrous sorbents of large surface area,

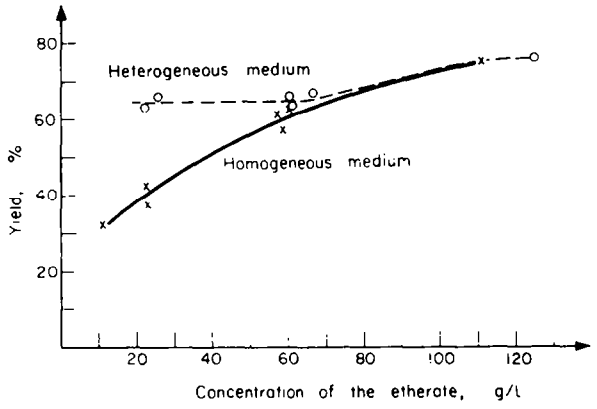


FIG. 1. The relationship between yield of [10]-α-cyclothien-1-one and $AlCl_3$ etherate concentration in homogeneous medium and in the presence of a coarce pore silica gel.

without preliminary hydrolysis of the former. Alumina and silica gel were selected to illustrate the behaviour of such sorbents. The authors believe that the solid phase is able to absorb the molecules undergoing cyclization. This causes a sharp fall in the mobility of the latter and facilitates thereby the intramolecular course of the acylation process. In this connection it is noteworthy that finely dispersed silica gel with an average pore diameter less than 15 Å has no effect on the acylation probably due to this sorbent being unable to adsorb the large molecules of the reactant.

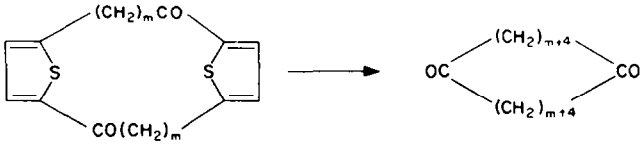
A characteristic feature of the cyclization reaction in the presence of a sorbent is that over a wide range of values the $AlCl_3$ etherate concentration has no appreciable effect on the yield of the acylation product (as established on the example of the conversion of 10-(thienyl-2)capryl chloride into [10]-α-cyclothien-1-one.[48] The relationship between yield of [10]-α-cyclothien-1-one and $AlCl_3$ etherate concentration in a homogeneous medium and in the presence of a sorbent (coarse pore silica gel) are given in Fig. 1.

As stated above the authors carried out the intramolecular acylation in the presence of $AlCl_3$ etherate, either alone or in combination with a solid phase, such as aluminium oxychloride, alumina or silica gel. Since the vacant orbital of aluminium in the etherate is occupied by an electron pair from the ether oxygen, it may be assumed that this oxonium complex participates in the acylation reaction only because of dissociation of the complex into its components. However no absorption bands characteristic of ethers (1120 cm^{-1}) could be observed in the IR spectra of chloroform

solutions of $AlCl_3$ etherate over the concentration range 0·2 to 1 molar.[49] In all probability in the reaction of the acid chloride with the etherate the ether molecules are replaced by acid chloride leading to an acid chloride–aluminium chloride complex. This is supported by the observation that on adding an aliphatic acid chloride (pelargonyl chloride) to a chloroform solution of $AlCl_3$ etherate the 1120 cm^1 ether band appears in the IR spectrum.

In order to transform the bi- and tricyclic thiophene ring systems into many-membered alicyclic compounds, use was made, as stated earlier, of the reductive desulphurization method with Raney nickel.[50] This reaction has considerable preparative application, in transforming thiophenic compounds into aliphatic hydrocarbons, acids, alcohols, ketones, ethers, amines, amino alcohols, amino acids etc. (for bibliography see Ref. 51) under very mild conditions.

Optimal conditions have been developed for the reductive desulphurization of α-cyclothieneones in which sulphur is removed and the double bonds are reduced without affecting the carbonyl group. This reaction was carried out by heating the thiophene derivative for 2–3 hours at 30–50° with Raney nickel in a benzene–ethanol mixture to which acetone was added as solvent. Yields of the many-membered cycloaliphatic ketones amounted to 70–90% based on the thiophene ketones. By reductive desulphurization of the corresponding α-cyclothieneones (XVII, n = 14–17) the authors obtained (cf. p. 10) cyclotetradecanone, exaltone, cyclohexadecanone and dihydrocivetone. From α-cyclodithienediones (XXII, m = 5,8,9), the higher cyclic diketones—cycloeikosane-1,11-dione, cyclohexakosane-1,14-dione and cycloöctakosane-1,15-dione* (XXIX, m = 5,8,9)—were prepared.



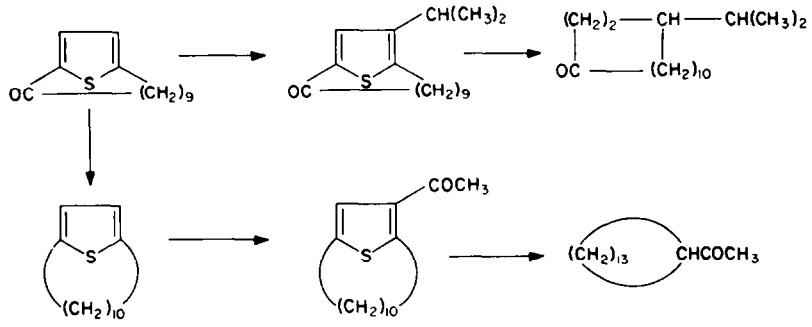
XXII XXIX

The use of thiophene as starting material in the synthesis of cyclic compounds not only simplifies construction of the long aliphatic carbon chain and facilitates the ring closing process, but, as has already been pointed out also makes it possible to prepare many-membered alicyclic systems with various substituents that are difficult to incorporate in the preformed alicyclic molecule. Such possibilities were studied by the synthesis of acetylcyclotetradecane and γ-isopropylcyclotetradecanone (Scheme 5).

In general, other heterocycles besides thiophene could be utilized for such a reaction and other desulphurization reagents besides Raney nickel could be of value. However, at present the most extensive and real possibilities are afforded by the

* This conversion is a strict proof of the structure of the initial compounds of the thiophene series, since the resultant alicyclic diketones have been obtained earlier by an independent method[52]. Therefore, there are no grounds to the affirmation by Shuetz and Baldwin[39] that no structure proof of the compounds obtained had been presented in our first short communication.[39]

[49] L. I. Belen'kii and B. V. Lopatin, *Izvest. Akad. Nauk SSSR, Otdel Khim. Nauk*, N 5, 934 (1963).
[50] J. Bouglaut, E. Cattelain and P. Chabrier, *Bull. Soc. Chim. Fr.* (5), **6**, 34 (1939).
[51] Ya. L. Gol'dfarb, B. P. Fabrichnyi and J. F. Shalavina, *Tetrahedron* **18**, 21 (1962).
[52] L. Ruzicka, M. Stoll, H. W. Huyser and H. A. Boekenoogen, *Helv. chim. Acta* **13**, 1152 (1930).



Scheme 5

Raney nickel desulphurization of the thiophenic compounds. At the same time, no doubt, other methods will be developed for the cleavage of various heterocyclic systems. One may call to mind that two or three decades ago an important direction in heterocyclic chemistry was the search of methods for preparing heterocycles by ring closure of linear compounds. Now another direction is assuming more and more importance; namely the cleavage of heterocycles which as one can see from the example of the thiophene derivatives opens new routes to aliphatic and alicyclic compounds.