The Place of Dibenzo[*b*,*f*]thiepin Derivatives in Medicinal Chemistry: Structures and Activities [a]

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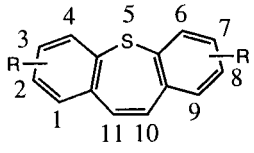
Contents

1. Introduction.

Derivatives of dibenzo[*b*,*f*]thiepin **1** or its 10,11-dihydro derivative **2** appear in chemical literature since 1957 [1]. Their chemistry up to 1971 was carefully reviewed by Traynelis [2]. Because of the important participation of the author's research team in this field, he tried to complete the mentioned review in a lecture at the 6th International Congress of Heterocyclic Chemistry in Tehran [3]. This lecture, however, was limited mainly to the chemistry of the author's team and in the medicinal chemistry line only to CNS activities. In the present review, the description of chemistry (mostly outlined in references [1,2]) will not be cited. Contributions of all teams working in the field will be reported and the main attention will be devoted to the medicinal aspects in all lines of biological activities described (without pharmacological and clinical details which are available in the cited papers).



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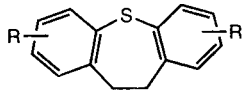

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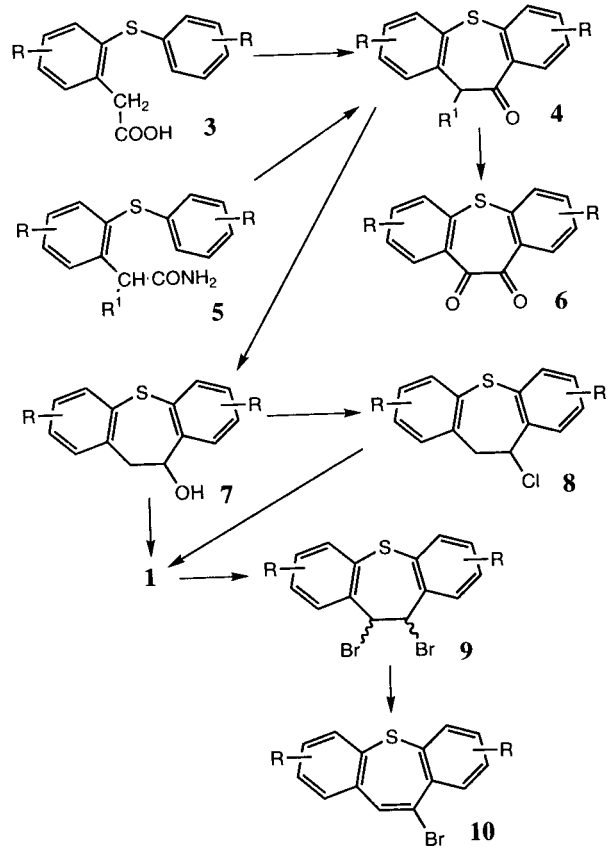
2. Useful Intermediates.

The main synthetic method, serving as the entry to the whole field, has to be specified first: it is the modified Friedel-Crafts cyclization of 2-(2-arylthiophenyl)acetic acids **3** to ketones **4**. This was used earlier by Loudon [1] in 1957 and the most useful practice consisted in heating with polyphosphoric acid [4,5]. Some special cases required different cyclization procedures: heating with

Scheme 1

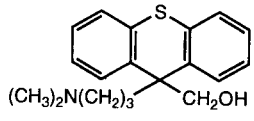


polyphosphoric acid and toluene under vigorous stirring [6], trifluoroacetic acid anhydride at room temperature [7], hydrogen fluoride at room temperature [8], methanesulfonic acid and phosphorus pentoxide in boiling 1,1,2,-2-tetrachloroethane [9] *etc.* Instead of the acids **3**, their chlorides could be used and cyclized with aluminium chloride [4,10]. The acid amides [5], even with an α–substituent, were easily cyclized with polyphosphoric acid [11,12] to the ketones **4**, including their 11-substituted derivatives [13].

Some general reactions leading to further useful intermediates are: Ketones **4** were oxidized [4,14,15] (*e.g.* with selenium dioxide) to diketones **6** and reduced with complex hydrides [5,14,16] to alcohols **7**. These were converted by treatment with hydrogen chloride [5] or thionyl chloride [16] to the very reactive chloro compounds **8**. The acid-catalyzed dehydration [5] of alcohols **7** or elimination of hydrogen chloride from **8** (proceeding as a side reaction in all substitution reactions of **8** with amines [17]) afforded the quasi-aromatic compounds **1**. Addition of bromine led to mixtures of stereoisomeric dibromides **9** which were dehydrobrominated to monobromo compounds **10** [17-20].

3. Neurotropic 10-(Aminoalkyl) Compounds.

The priority in the medicinal line in this field belongs to Smith Kline and French by a patent [21] describing the synthesis of the amine **12** from thioxanthenemethanol **11** by Wagner-Meerwein rearrangement. It was stated that the product had central stimulant, antihistamine and antispasmodic activity.



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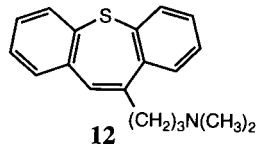

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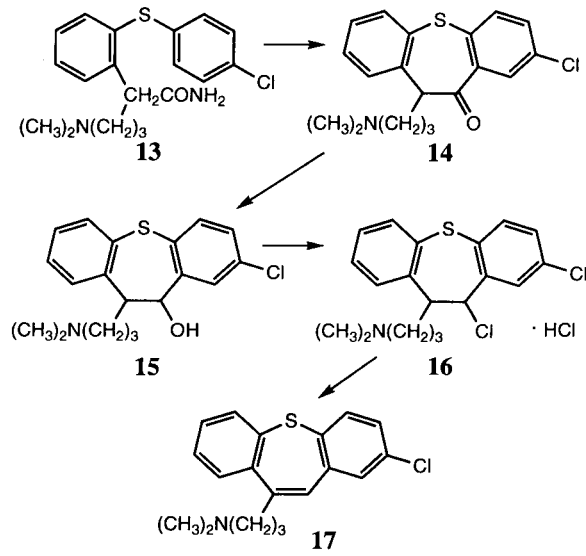
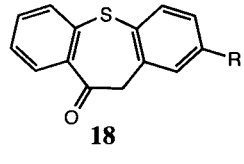
Similar chlorinated amines were described more recently by Smrž *et al.* [13]. Cyclization of the amide **13** with polyphosphoric acid resulted in the amino ketone **14** showing CNS depressant, antireserpine, hypothermic and antihistamine effects - in fact the profile of a potential antidepressant. The work continued by reduction of **14** to the alcohol **15** (*cis*-isomer) having anticholinergic (spasmolytic and mydriatic) activity. The following reaction with thionyl chloride resulted in the hydrochloride **16** which was dehydrochlorinated with potassium hydroxide to **17** showing properties of a potential neuroleptic agent with central depressant, slight cataleptic, adrenolytic and antihistamine effects.

The team of Geigy [22] described the synthesis of the saturated amines **19** from ketones **18** in six steps starting with the addition to acrylonitrile, including the removal of the oxo group with hydrazine and using in the last step reduction of the corresponding dimethylamide with lithi-

Scheme 2



um aluminium hydride. The product **19** (R = Cl) was described as an antihistaminic agent being more active than promethazine. 10-(1-Methyl-4-piperidyl)-10,11-dihydrodibenzo[*b,f*]thiepin [17] and its 8-methoxy derivative **6** (obtained by reactions of **8** with 1-methyl-4-piperidylmagnesium chloride) revealed an extremely high central depressant activity in several tests. Similar compounds and their unsaturated analogues were described by Fouché *et al.* [23,24] and characterized as neuroleptics and tranquilizers with important antihistamine, antiserotonin, antispasmodic, and antiemetic activities. Aminoketones like **14** were also prepared by the Geigy team [25] and among them especially the 11-(3-methylaminopropyl)dibenzo[*b,f*]thiepin-10(11*H*)-ones showed properties of potential antidepressants [26,27].



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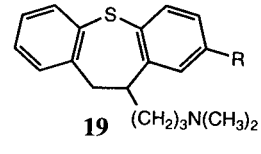

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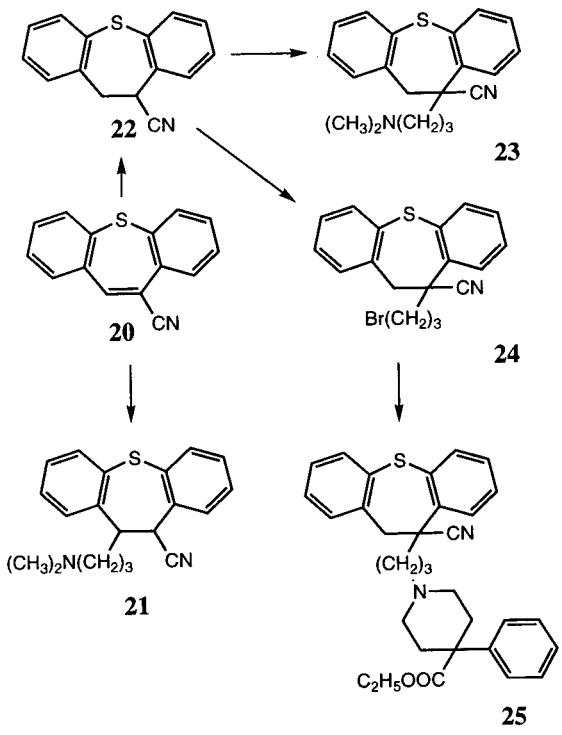
Much more recently, Šindelář *et al.* [20] described the synthesis and properties of several interesting amino nitriles: The starting bromo compound **10** (R = H) was converted by heating with cuprous cyanide in dimethylformamide to the nitrile **20** which reacted with 3-dimethylaminopropylmagnesium chloride in a 1,4-addition reaction and after hydrolysis afforded the aminonitrile **21** as a *cis-trans*-mixture, separated by crystallization of the oxalates. The major *cis*-isomer was found to have antireserpine activity being thus a potential antidepressant. Reduction of **20** with sodium borohydride gave the saturated nitrile **22** which by alkylation with 3-dimethylaminopropyl chloride afforded the aminonitrile **23** showing

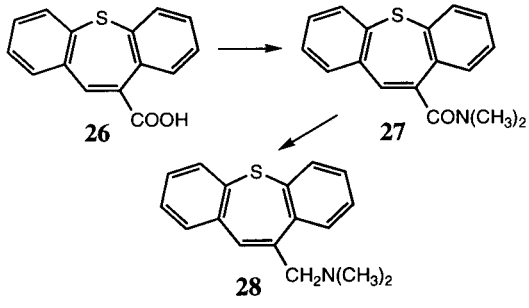
central depressant, analgesic and some cardioavscular activity. In an effort to search for new analogues of the antidiarrhoic agent diphenoxylate [28], the nitrile **22** was converted *via* the bromopropyl intermediate **24** and by its reaction with norpethidine to compound **25** which showed a significant inhibitory effect toward diarrhoea, elicited in mice by intravenous administration of serotonin.

Scheme 3



The Geigy team described in patents [29-31] a series of 10-(aminomethyl)dibenzo[*b,f*]thiepins with damotepine [28] as the selected compound [32]. One of the synthetic routes [31] consisted in alkaline hydrolysis of nitrile **20** to the acid **26** which in two steps afforded the dimethylamide **27**. Its reduction with lithium aluminium hydride gave **28**. The compound was characterized pharmacologically as a sedative, narcosis potentiating, sleep inducing and adrenolytic agent [32]. Phase I clinical trial [33] in healthy volunteers indicated for damotepine antidepressant and anxiolytic properties similar to those of doxepin. Because of unfavourable pharmacokinetics [34] and high dosage necessary, its further development was discontinued.

Scheme 4



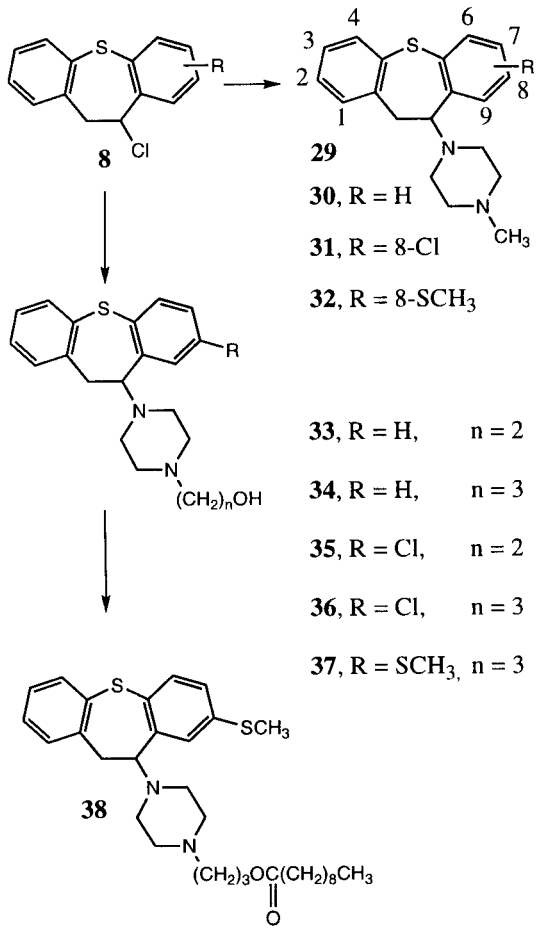
4. 10-(1-Piperazinyl) Derivatives.

4.1. Perathiepin Series: Octoclothepin, Methiothepin.

An important turn in the field in 1964 was the discovery [35-39] of the piperazinyl derivatives **29** which were accessible from the ketones *via* chlorides **8** in three simple steps; the whole group was identified as multipotent neuro- and psychotropic agents with predominant neuroleptic character. Even the nuclearly unsubstituted perathiepin [30], prepared by Jílek [5,17], proved a major tranquilizer surpassing in activity the well known chlorpromazine [40]. The compound passed successfully the whole preclinical stage and in 1965 was made available to clinicians. Czech psychiatrists [41-43] confirmed its neuroleptic character and in several cases its antipsychotic action in schizophrenic patients. This effect, however, was not reliable, *i.e.* perathiepin did not act in the majority of patients. It was clear that it must be considered a lead compound only which necessitated structural optimization. Substitution of *N*-methyl with other groups only in cases of hydroxyalkyls (compounds **33** and **34**) maintained the activity [17]. The structure of chlorpromazine with its chlorine atom indicated an additional approach. Systematic introduction of chlorine atoms into the eight possible positions in the aromatic rings [35,44-47] resulted in finding the important more potent octoclothepin (clorotepine, **31**), the 8-chloro derivative [11,48-50]. Octoclothepin proved much more potent than chlorpromazine and perathiepin [50-52] in the main lines indicating antipsychotic activity: ataxia, antiamphetamine action, hypothermic effect, catalepsy-inducing and antiapomorphine activity in rodents [53-56]. After preclinical studies which included pharmacokinetic and metabolic investigations [57-65], helped by many standards synthesized for comparison [66-71], the drug was clinically tested for several years in oral form (hydrogen maleate), in drops and injections (aqueous solution of the methanesulfonate and solution of the base in vegetable oil) [72,73]. In several open and controlled clinical trials, its high antipsychotic action and safety was confirmed [74-88]. Its manufacture was started [89] in 1971 and the drug (Clotepin^{R}) has successfully been used (oral dosage of 10-175 mg/day) in Czechoslovakia for 20 years.

The chiral centre in the octoclothepin molecule led to its resolution by Jílek [48,90] and more recently by Bogeso [91]. The intervention of the Wander-Sandoz team resulted in finding stereoselectivity of octoclothepin action [92-94] and in determination of absolute configuration of the more active (+)-enantiomer [95,96], which was (*S*). Some conclusions of theoretical medicinal chemists

Scheme 5



in this case are important even if partly contradictory. Seeman [97] found that the stereoselectivity ratio of (*S*)(+)- and (*R*)(-)-octoclothepin in antidopaminergic tests *in vitro* was only 11:1 and explained it by the fact that the molecule of octoclothepin (**31**) is much more flexible than that of the sterically rigid neuroleptic agent butaclamol (used for comparison). In agreement with that, Náhunek [98], who compared clinically both enantiomers, found that even the (*R*)(-)-enantiomer in higher dosage had clear antipsychotic activity. Bøgesø [91] summarized the octoclothepin case as follows: (*S*)(+)-Enantiomer is clearly more potent as a dopamine D2 antagonist but the (*R*)(-)-enantiomer still had significant D2 antagonistic action. Both enantiomers were equally active in test models indicating activity at D1 receptors, serotonin 5-HT2 receptors and α1 adrenoceptors. The noradrenaline uptake inhibition was confined solely to the (*S*)(+)-enantiomer. Overall, the (*S*)(+)-compound had a classical neuroleptic profile, while the (*R*)(-)-compound had a more atypical profile which was in agreement with the Náhunek's clinical findings [98]. Conformations of both octoclothepin enantiomers were repeatedly discussed in connection with the topography of the neuroleptic (dopamine D2) receptor [99-103].

The molecule of octoclothepin (**31**) was modified in many ways. From the *N*-substituted and piperazine-modified analogues [90,104-109], the amino alcohols **35** (noroxyclothepin) [110] and **36** showed high activity [104]. Fourty-five analogues with different substituents in position 8 were prepared out of which the iodo [111], methoxy [6], ethoxy [112], methylthio [6], ethylthio [113], dimethylsulfamoyl [114], methylseleno [115], nitro [116,117], amino [116], dimethylamino [118], methyl [6], ethyl, isopropyl and cyclopropyl [7], trifluoromethyl [8], cyano [119], formyl, acetyl and propionyl [120] substituted compounds showed activity comparable with that of octoclothepin or even higher. The effect of aromatic substitution on neuroleptic activity was recapitulated several times [121,122] including two QSAR studies [123,124]. A condensed review of this area with complete list of references was published [125].

The 8-methylthio derivative **32**, called methiothepin (metitepine) [6,126], attracted the interest of the Hoffmann-La Roche research groups where a modified synthesis was elaborated [127]. The agent was developed as a potent neuroleptic until the stage of clinical tests which were stopped due to frequent side effects [128]. The Roche biochemical pharmacologists [129-131] identified methiothepin as an extremely potent central serotonin antagonist which made this compound a tool in many neurochemical and neuropharmacological investigations [*e.g.* 132-135]. Its metabolism, which proceeded mainly in the lines of *N*-demethylation, *S*- and *N*-oxidation, Ar-hydroxylation and combination of these attacks, was very carefully studied [136] and a number of metabolites was identified. The synthesis of several potential metabolites as standards [6,66,104,137-140] was carried out. Methiothepin is evidently manufactured on a small scale for experimental purposes by BIOMOL Research Laboratories [141]. Kyburz *et al.* [128] carried out the resolution of racemic methiothepin and announced the lack of stereoselectivity of its action, evidently mainly on the basis of comparison of the central depressant effects of the enantiomers. The medicinal chemists at the Merrell Dow Research Institute in Strasbourg [142,143] repeated the resolution and found stereoselectivity of action (antagonism) at the central serotonin recognition site. For the more active (-)-enantiomer, the absolute configuration (*R*) was suggested.

4.2. Amino Alcohols and Esters: Oxyprothepin and Oxyprothepin Decanoate.

A structural combination of methiothepin (**32**) and the amino alcohols **33-36** is represented by oxyprothepin (**37**) which belongs to the most active members of the series [104,144-146] and passed all stages of preclinical research: pharmacology [147-152], pharmacokinetics and

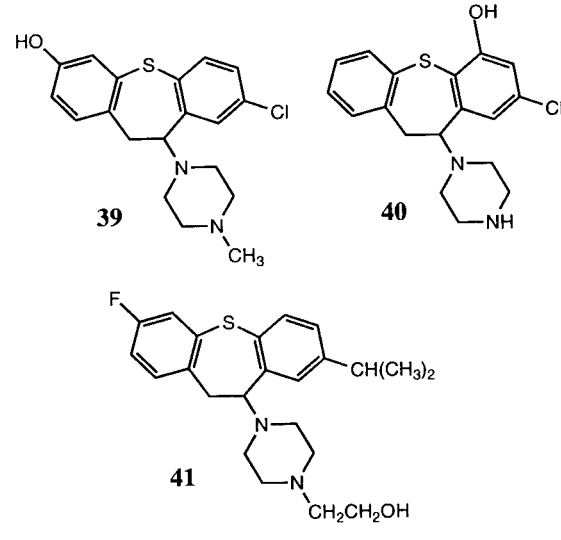
metabolism [153-158], synthesis of potential metabolites [66,138-140,159,160]. Clinical testing included a study in healthy volunteers [161], open clinical trials in patients suffering from schizophrenia, mania and depression [162-166] and finally comparative clinical trials with perphenazine [167], chlorpromazine [168], octoclothepin [169-173] and haloperidol [174,175]. Since the late seventies, oxyprothepin methanesulfonate (Meclopin^R) has been used in Czechoslovakia for pharmacotherapy of psychoses (oral dosage of 15-50 mg/day) and substituted octoclothepin.

Oxyprothepin (**37**) and similar amino alcohols (*e.g.* **33**) were found a good basis for development of ester depot neuroleptics in the dibenzo[*b,f*]thiepin series for intramuscular use [176]. Such esters [177-180] were prepared by esterification of the amino alcohols by treatment with chlorides of lipophilic acids or better with free acids; for modified synthetic ways, *cf.* [139]. The first esters, considered clinical candidates, were noroxyclothepin decanoate [181,182] and oxyprothepin enanthate [183,184]. The selected ester was oxyprothepin decanoate (**38**) whose pharmacology [185-188] and esterolytic cleavage in serum and muscle tissue [189] were investigated. Its clinical testing [190-195] proved excellent usefulness in the long-term maintenance treatment of schizophrenic psychoses. Extensive clinical comparison with fluphenazine decanoate [196-199], fluspirilene [200], perphenazine enanthate [201] and clopentixol decanoate [202] resulted in 1984 in the introduction of oxyprothepin decanoate (Meclopin inj.^{R}) into the Czechoslovak market: a single intramuscular injection of 25 mg in an artificial oil (Miglyol^R) exerted its action for 3-4 weeks.

4.3. Fluorinated Perathiepin Derivatives.

Extensive studies of the metabolism of neuroleptic agents belonging to the 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin series and especially of octoclothepin (**31**) resulted in the finding that 3-hydroxyoctoclothepin (**39**) (being a strong neuroleptic agent) [67] and 6-hydroxynoroctoclothepin (**40**) [69] (both compounds obtained by demethylation of the corresponding methoxy analogues with boron tribromide in the last step of synthesis) are metabolites of octoclothepin [61-64]. Metabolic hydroxylation in other positions could not be excluded. On the basis of the hypothesis that blocking positions of metabolic hydroxylation with fluorine atoms could retard metabolization of the active compounds and their elimination, systematic introduction of fluorine atoms (proceeding in the stage of aromatic intermediates) into all accessible positions of molecules of compounds belonging to the perathiepin series was carried out [203,204]. The products were tested using oral administration not only from the point of view of acute effects but also the duration of the effects (ataxia in mice, catalepsy in rats, antiapomorphine actions in rats and dogs) was checked. In this context, derivaties of **30** and **33** fluorinated in the following positions were prepared: 2 [205-207], 3 [9,12,205,206,208-213], 2,3 [214], 6 [215], 7 [216-219], 3,7 [209,218] and 6,9 [220]. The optimum combination of the intensity of effects and their duration was attained with the 3-fluorinated compounds having in position 8 one of the following "neuroleptic" substituents: Cl [12,205], F, Br and I [210], CH_3, C_2H_5 and $CH(CH_3)_2$ [213], CF_3 [9], OH, OCH_3 and OC_2H_5 [211], SCH_3 [206], SC_2H_5 [211], NO_2, NH_2, $SO_2N(CH_3)_2$ and $COCH_3$ [213].

The final choice was the 3-fluoro-8-isopropyl compound **41** which was called isofloxythepin [203,204,221-223] and which underwent first all stages of preclinical research (with participation of the Japanese scientists): behavioural pharmacology [224-229], biochemical pharmacology [230-242], toxicology [243], pharmacokinetics [244-249] and metabolism [221,250,251]. Clinical studies, lasting for five years [252-258], resulted in the finding that the drug in a single oral dose of 2-5 mg revealed its antipsychotic (mainly antischizophrenic) effect for 2-7 days. Isofloxythepin (**41**) was approved in Czechoslovakia for human use but the relatively complicated manufacturing process prevented until now production and marketing. The action of isofloxythepin is stereoselective and the (-)-enantiomer (absolute configuration unknown) was found to be the active component of the racemate from the point of view of dopamine D2 antagonism [221, 259-261]. Isofloxythepin decanoate was found an ultralong depot neuroleptic: an intramuscular dose of 5 mg/kg blocked the apomorphine-induced vomiting in dogs for 6 weeks [262].

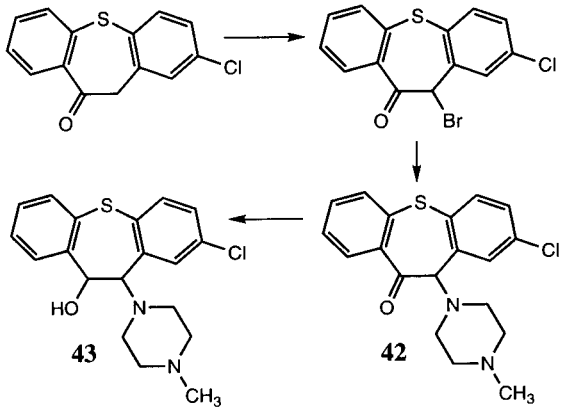


4.4. 11-Oxo-10-piperazino Compounds.

Using the synthesis shown in Scheme 6, the Geigy team [263] patented the preparation of the piperazino ketone **42** and its reduction to the piperazino alcohol **43** [264] for

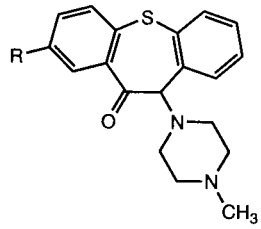
which central depressant, antiemetic, narcosis potentiating and anticonvulsant activities were claimed. Compound **42** with the code mark **GP-45795** was selected as a potential antipsychotic agent for clinical testing. This proved its antipsychotic character [265,266] but its development was evidently discontinued [267]. Similar piperazino ketones **44** and **45** and the corresponding alcohols were prepared independently [90,112,268-270] but because of the rather low activity, they were not studied in detail.

Scheme 6



4.5. Piperazine Enamines.

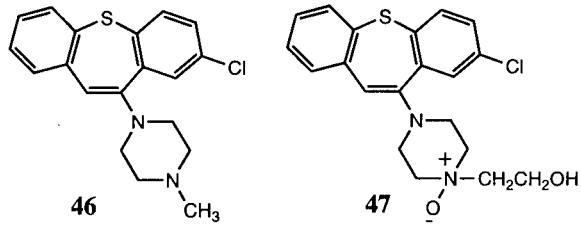
In the period 1969-1974, the Japanese company Fujisawa applied for patents [271-273] for protecting the series of piperazine enamines like **46** (dehydroclothepin) which were prepared from ketones **4** by treatment with *N*-methylpiperazine and analogues in the presence of titanium tetrachloride [270]. The enamine series was also reported in patents of Richardson-Merrell Co. [274]. The compounds were characterized as potent sedative and neuroleptic agents. The Prague group [275-277] arrived independently at the enamine series using the classical Stork method (reaction of ketones **4** with the piperazines in the presence of 4-toluenesulfonic acid in boiling xylene with continual removal of the water formed). This method required long reaction times and the yields were low. Modification, consisting of heating mixtures of **4** with piperazine monotosylates *in vacuo* to 200°C [48] produced the enamines very quickly in almost quantitative yields. Dehydroclothepin [46] proved more active than octoclothepin especially in tests for cataleptic and anti-apomorphine actions in rats [276]. Many similar and potent enamines were prepared (mostly by the superior titanium tetrachloride method) [7,113,114,178,205,213,-217-219,251,276,278] but none found practical use. The *N*-oxides of **46** and analogues were claimed in a Hoffmann-La Roche patent [279] to be very potent tranquilizers. The *N*-oxide **47**, prepared by Jílek *et al.* [179], was described as a case of dissociation of both main lines of



44, R = H

45, R = OCH_3

activities in this series: more than 10 times stronger cataleptic than octoclothepin and 10 times weaker as a tranquilizer. The enamines (type **46**) are convertible to the 10,11-dihydro compounds **29** by reduction either with zinc in acetic acid [270] or with sodium borohydride and acetic acid in tetrahydrofuran [127]. For some specifically substituted **29** (where the chloro intermediates **8** were too unstable), synthesis *via* the enamines was the only possibility [118,280,281].



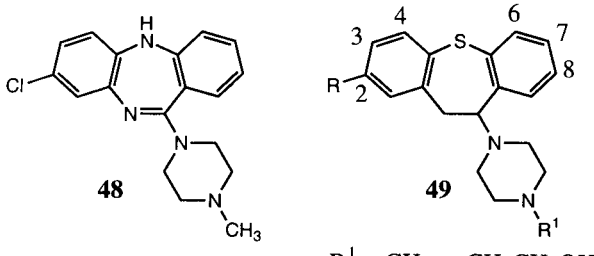
4.6. Noncataleptic Perathiepin Derivatives.

After concentration to highly cataleptic substances in the piperazinodibenzo[*b,f*]thiepin series, it became evident that catalepticity is connected with the unwanted extrapyramidal side effects of neuroleptics in patients. The Wander-Sandoz compound **48** (clozapine), a piperazinodibenzo[*b,e*][1,4]diazepine with the chlorine atom in a seemingly wrong position, proved noncataleptic but had evident antipsychotic activity [282]. This was the starting point of the search for noncataleptic antipsychotics [283]. The Prague group participated in this programme and tried to reach the goal by shifting the "neuroleptic substituent" from position 8 of dibenzo[*b,f*]thiepin into the quasi-symmetrical position 2 [283]. A number of compounds **49** with the following pattern of substituents was synthesized: 2-Cl, 2-F, 2-Br, 2-I, 2-Cl-7-F, 2-Cl-8-F [284], 2,3-Cl_2 [285], 2,4-Cl_2 [286], 2,6-, 2,7- and 2,8-Cl_2 [287], 2-Cl-7-OCH_3, 2-Cl-7-OH [288], 2-Cl-8-OCH_3 and 2-Cl-8-OH [289], 2-CH_3 [290], 2-NO_2, 2-OCH_3 and 2-OH [291], 2-NH_2, 2-$NHCOCH_3$ and 2-$COCH_3$ [292], 2-SCH_3, 2-$SO_2N(CH_3)_2$, 2-CF_3 and 2-OCH_3-8-F [293], and finally 2-Hal-8-$CH(CH_3)_2$ [294]. Only the 2-halogeno compounds fulfilled the demanded qualities: (1) none or very low cataleptic effect, (2) more or less central depressant activity, (3) antidopaminergic activity *in vitro* proven by an increase of dopamine metabolism in the rat brain striatum (increase of the homovanillic acid level). Out of the last named series [294], the 2-iodo-8-isopropyl compound **50** corresponded to these conditions but the

presence of the atom of iodine in the molecule prevented its selection and docloxythepin (**51**) became the clinical candidate [283,295].

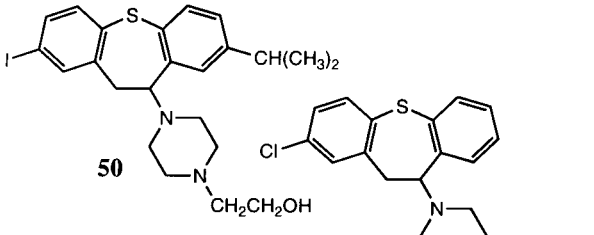
The synthesis of docloxythepin used all of the approaches mentioned for similar compounds [19,284,296]. Pharmacological investigations (including biochemical pharmacology) [297-303] resulted in recommendation of clinical testing. Studies of pharmacokinetics and metabolism [304-307] completed the information necessary. Clinical testing [253,308] proceeded only in phase I (healthy volunteers) and was discontinued in view of the suspected hepatotoxicity in dogs [309].

The second "noncataleptic" clinical candidate of the Prague group was cloflumide (**52**) which was selected on the basis of its surprisingly low toxicity [310-313] and which passed only a part of preclinical studies [314-316]. The finding of some catalepticity in a more detailed study led to termination of its development [251].

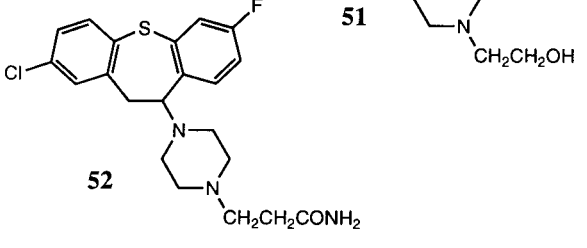


48 **49**

$R^1 = CH_3$ or CH_2CH_2OH

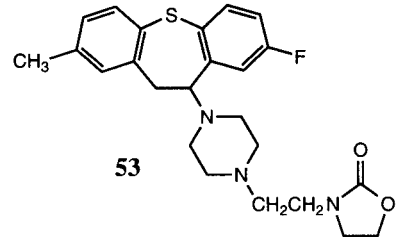


50 **51**



52

The Hoffmann-La Roche team devoted much effort to finding noncataleptic antipsychotics in the piperazinodibenzo[*b,f*]thiepin series. Variously Ar-disubstituted derivatives of **30**, **33** and **34**, described in patents [317-320], as well as their *N*-propargyl analogues [321], evidently did not fulfil the expectations. Introduction of 2-(2-oxooxazolidino)ethyl as *N*-substituent [322] led to more interesting compounds and **53** (**Ro 11-9198**) became the clinical candiate [323]. The racemic compound was resolved [324, 325] and the (*S*)(+)-enantiomer (absolute configuration determined by X-ray diffraction) was found to be the active principle. Its pharmacological profile was established in tests showing the influence on homovanillic acid concentration in rat brain, inhibition of adenylate cyclase, inhibition of conditioned reflexes in rats and inhibition of apomorphine-induced emesis in dogs. The compound proved low toxicity, very low cataleptic activity and strong tranquilizing effect. Allegedly, it was clinically tested in schizophrenic patients using oral doses up to 300 mg/day but because of unreliable effects, the clinical experimentation was stopped.

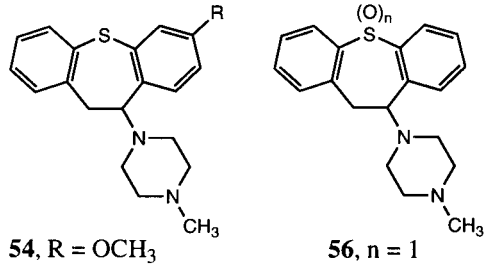


53

4.7. Perathiepin Analogues With Various Activities.

Compounds of the perathiepin series were found to show in addition to the neuroleptic effects many other activities. Some of them, *e.g.* the adrenolytic and hypotensive effects, were considered unwanted side effects. On the other hand, some other activities, which might predominate over the pharmacological spectrum, could be the basis of potential utility in the corresponding fields of pharmacotherapy. Antihistamine effects are common for the whole field but in some cases dominates and is usually accompanied with the central depressant effect. Examples are the 7-substituted derivatives of **30**, especially the 7-methoxy compound **54** [280] and the methyl compound **55** [326]. Fouché claimed in patents [327,328] important antihistamine activity for perathiepin *S*-oxide (**56**) and perathiepin *S,S*-dioxide (**57**).

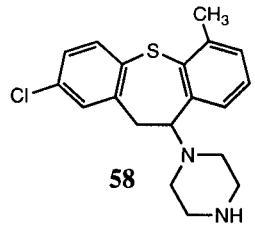
On the basis of some analogies, compound **58** and some analogues were designed as potential antidepressants and synthesized [329]; they were found devoid of antireserpine as well as of cataleptic activity and were thus neither antidepressants nor neuroleptics.



54, R = OCH_3 **56**, n = 1

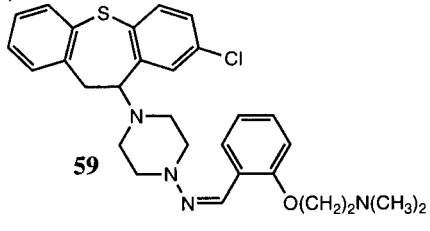
55, R = CH_3 **57**, n = 2

On the basis of some structural similarity with the structure of the anticonvulsant agent ropizine, a series of

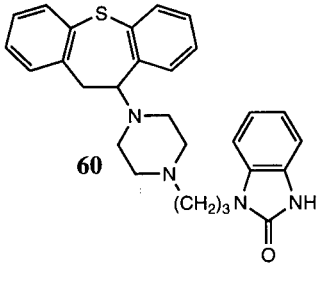


58

hydrazones like **59** was synthesized [330]; the expected anticonvulsant activity against pentetrazole was confirmed only in high doses. Compound **60**, designed as a potential antiallergy agent analogous to oxatomide, proved in the test of passive cutaneous anaphylaxis more potent than oxatomide [331]. The Dainippon team [332] described the *N*-cinnamyl analogue of perathiepin (**61**) and mentioned its protective activity against complete ischemia, lipid peroxidation and convulsions. A Hoffmann-La Roche patent [333] protected a combination of dehydroclothepin (**46**) with 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone as an antiinflammatory medicament. Many members of the perathiepin series showed antimicrobial activity *in vitro* against a broad spectrum of microorganisms [334]. Compound **62** and the corresponding enamine showed specific antifungal activity against a series of Saccharomyces species [335]. The antituberculous activity *in vitro* was so constantly connected with derivatives of **30** that it warranted a special QSAR study (336).



59



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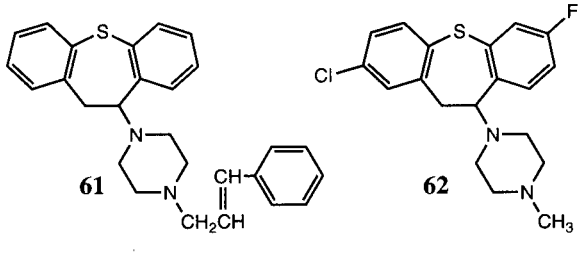
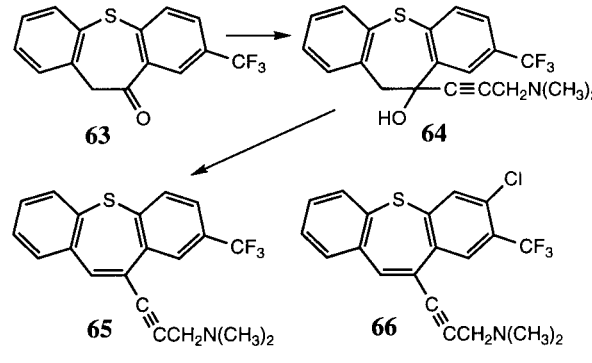


61 62

5. 10-(Aminoalkynyl) Compounds.

On the basis of structural topology (measurement of the distance between the basic side chain nitrogen atom and the centre of the closer aromatic ring on stereo-models constructed after X-ray studies), Kyburz *et al.* [337,338] designed a series of 10-(3-aminopropynyl)dibenzo[*b,f*]-thiepins with selected compound **Ro 11-7330** (**65**). Its synthesis proceeded from the ketone **63** by treatment with 3-dimethylaminopropynyllithium in liquid ammonia and the following dehydration of the intermediate **64**. Compound **65** was characterized [339] by marked blockade of central dopamine receptors: it effectively increased homovanillic acid level in rat brain but did not affect MOPEG levels. It blocked conditioned avoidance responses, induced catalepsy and reduced motor activity in mice and rats. It proved a dopamine receptor blocker of medium potency with little effect on serotonin receptors and virtually no effect on noradrenaline receptors. Preliminary clinical data indicated antipsychotic activity in schizophrenic patients with low incidence of sedation. The final result of clinical trials was not published but the compound was evidently abandoned. A similar compound **Ro 12-9469** (**66**) was described by Aoki (Nippon-Roche) [340] as an antifungal agent active *e.g.* against Candida albicans.

Scheme 7



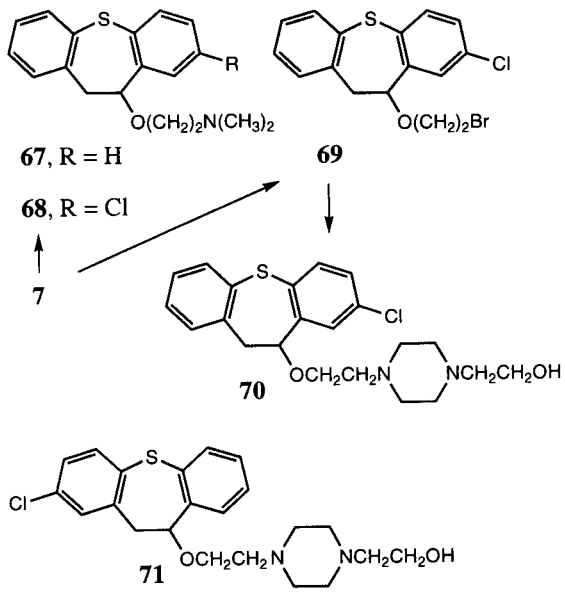
63 64 65 66

6. Aminoalkyl Ethers, Sulfides and Amines: Zotepine.

Simple aminoalkyl ethers like **67** and **68** were prepared from the alcohols **7** by treatment with sodium amide and 2-dimethylaminoethyl chloride in toluene [5,6,11,44]. The first **67** showed potent antihistamine activity, the other, **68** was a neuroleptic with strong central depressant activity but in general less active than octoclothepin (**31**). Bártl *et al.* [341] continued this work and by introduction of the piperazine moiety into the side chain came to compound **70**: a neuroleptic with an interesting activity profile - low toxicity, strong central depressant and antiapomorphine effects, mild cataleptic, intensively increasing the homovanillic acid level in brain and almost completely lacking the adrenolytic effect. It was prepared *via* the 2-bromoethyl ether **69** which was obtained from **7** (R = Cl) by reaction with 2-bromoethanol in presence of boron triflu-

oride. Shifting the atom of chlorine to position 2 (analogous synthesis starting from 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol) led to compound **71**, called clopithepin [342,343]. This low-cataleptic compound was stopped still in the preclinical stage [251] because its activity profile did not differ much from that of chlorpromazine.

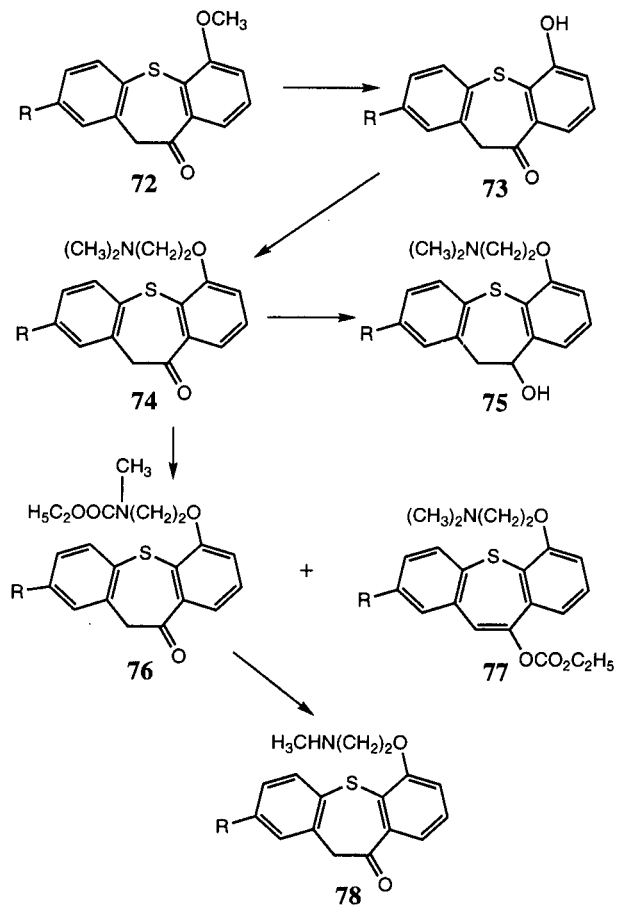
Scheme 8



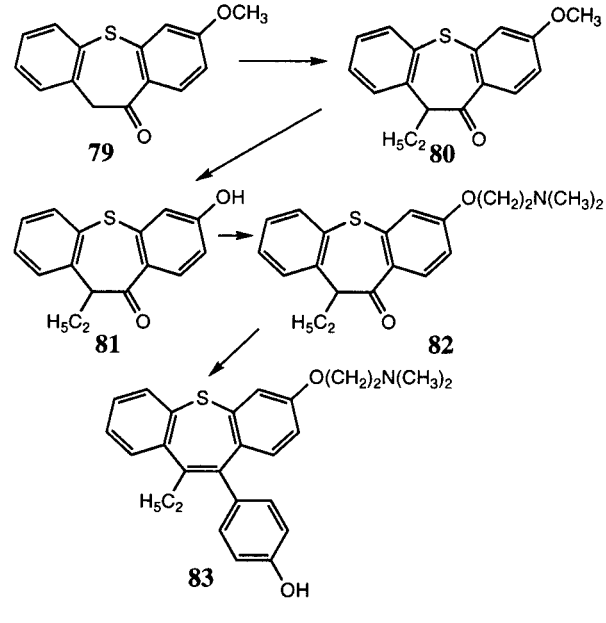
Two types of aromatic aminoalkyl ethers were described. Červená *et al.* [344] started from the methoxyketones **72** which were demethylated by heating with pyridine hydrochloride and the obtained oxophenols **73** were transformed to ethers **74** by reaction with 2-dimethylaminoethyl chloride in presence of sodium ethoxide. Reduction with sodium borohydride afforded the hydroxy ethers **75**. Treatment of **74** with ethyl chloroformate gave mixtures of **76** and **77**; the neutral carbamates **76** were hydrolyzed to give the secondary amines **78**. Compound **74** (R = H) was designed as a potential antidepressant; it really showed antireserpine effects together with tranquilizing, antihistamine, antispasmodic and especially antimicrobial activity.

The other type was represented by compound **83** which was prepared by chemists of Imperial Chemical Industries [345] and characterized as a potential antiestrogen. It proved good binding to rat uterine estrogen receptors *in vitro* and its antiestrogenic effect was shown in the antifertility and uterotrophic tests in rats. Its synthesis started from the ketone **79** and proceeded according to Scheme 10 *via* the intermediates **80-82**. The last step consisted in the treatment of the ketone **82** with 4-(2-tetrahydropyranyloxy)phenyllithium and the following acid-catalyzed dehydration and hydrolysis.

Scheme 9

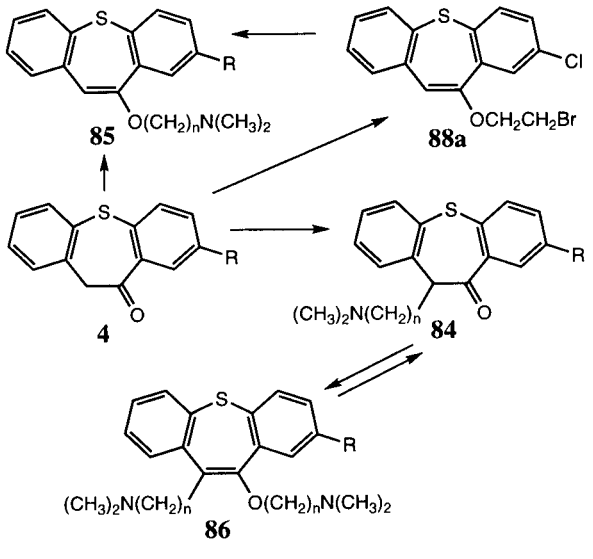


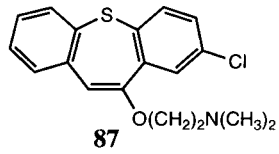
Scheme 10



In 1970 Jílek *et al.* [276] published a report on attempts to aminoalkylate ketones **4** (R = H, Cl) with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride in toluene in the presence of sodium amide. The aminoalkyl ketones **84** (R = H, n = 2; R = Cl, n = 3) were the minor products and the enol ethers **85** the major ones. The third type of products, identified as **86**, was evidently formed by further action of dimethylaminoalkyl chlorides on amino ketones **84** and the acid hydrolysis of these compounds was the cleanest process for preparing **84**. At that time, the enol ethers **85** were considered too unstable and therefore not of interest for use in therapy. Ueda *et al.* [346], belonging to the research of the Japanese Fujisawa Co., published eight years later a similar study which resulted in **zotepine** (**87**) as a potential neuroleptic agent. This paper [346] was backed by Fujisawa patents [347] already applied for 1968. Zotepine (**87**) was also accessible *via* compound **88a** [348]. A pharmacokinetic and metabolic study of zotepine [349] led to identification of several metabolites and four of them were obtained by synthesis [350-353]. Biochemical pharmacology characterized zotepine as a neuroleptic agent with affinity to central dopamine and serotonin receptors [354-360]. Behavioural pharmacology [361-367] showed similarity with chlorpromazine with less cardiovascular effects; toxicological investigation [368-371] proved possibility of use in pharmacotherapy. Clinical testing, carried out partly in Japan and partly in Europe, showed for zotepine [87] a rather unique profile with biphasic effect (activation and sedation), good antimanic effect, effect on negative symptoms of psychoses and low incidence of extrapyramidal side effects [372-387]. Zotepine was introduced into the market as **Lodopin**^{R} by Fujisawa in Japan and by Klinge Pharma in Germany [370] with recommended daily oral dosage of 75-150 mg.

Scheme 11

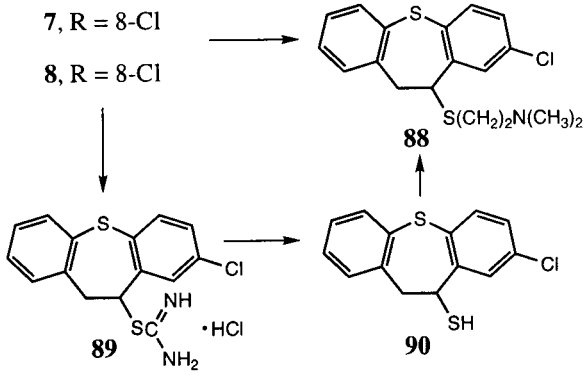




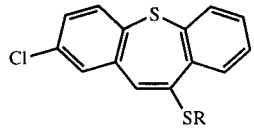
87

The American Hoechst-Roussel and the Prague team searched for potential drugs in the series of dibenzo[*b,f*]-thiepin 10-sulfides. Ong *et al.* [388] described the preparation of the sulfide **88** from the corresponding alcohol **7** by reaction with 2-dimethylaminoethanethiol hydrochloride in acetic acid in the presence of boron trifluoride. Bártl *et al.* [389] prepared the same compound **88** from the corresponding 10-chloride **8** *via* the isothiuronium salt **89** and the thiol **90**; the last step consisted in the reaction of the sodium salt of **90** with 2- dimethylaminoethyl chloride in ethanol. Compound **88** was found to have CNS depressant, anticonvulsant, antihistamine, anticholinergic and local anaesthetic activity.

Scheme 12



Valenta *et al.* [390] prepared similarly the thiol **91**. Its alkylation with 2-aminoethyl chloride afforded compound **92** which was transformed *via* the carbamate **93** to the 2-methylaminoethyl sulfide **94**. This compound showed a clear profile of a potential antidepressant. Similar properties were announced for **95**: it potentiated yohimbine toxicity in mice and had mild ataxic activity [391]. The car-

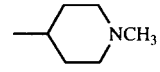


91, R = H

92, R = $CH_2CH_2NH_2$

93, R = $CH_2CH_2NHCOOC_2H_5$

94, R = $CH_2CH_2NHCH_3$

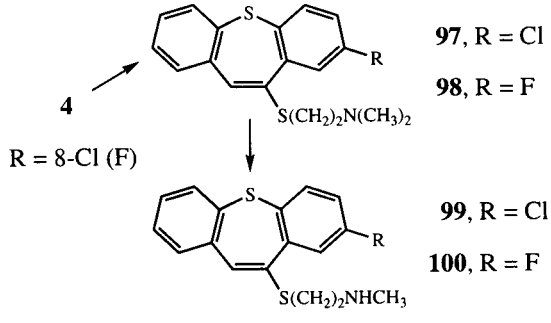
95, R = 

96, R = $CH(CH_3)COOH$

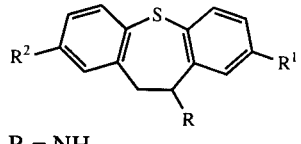
boxylic acids like **96** were found to have antiinflammatory activity (carrageenan and kaolin edema) and some analgesic activity in the writhing test in mice [390,392].

The ketones **4** could directly be transformed to the enol thioethers **97** and **98** [388,393,394] by treatment with 2-dimethylaminoethanethiol hydrochloride in acetic acid in the presence of boron trifluoride. Partial demethylation with phenyl chloroformate or cyanogen bromide and the following alkaline hydrolysis resulted in the methylamino compounds **99** and **100**. **The preferred** fluoro compound **100** showed antinociceptive potency in the pentazocine range as assessed by 2-phenyl-1,4-benzoquinone writhing and tail flick in mice. It was also twice as active as imipramine in preventing tetrabenazine-induced ptosis; it was characterized as a new type of antidepressant with important analgetic activity (394).

Scheme 13



In the group of amines with a direct bond of nitrogen to position 10 of the skeleton, the piperazino compounds have an exceptional position and they were, therefore, already treated. Simple amines, like amino **101**, methylamino **102** and dimethylamino **103** compounds, accessible by conventional methods [5,389,395,396], did not show important activities. For amino acids **104**, antiarrhythmic activity was claimed [397]. The 2-chloro substituted pyrrolidine **105** showed an almost complete spectrum of effects typical for antidepressants: antireserpine activity in three tests, potentiation of yohimbine toxicity in mice, inhibition of binding of [^{3}H] desipramine in rat hypothalamus [396]. Witiak *et al.* [398,399] described 10-(3-(ethylmethylamino)pyrrolidino) compounds **106** with two chiral centres in molecules. The compounds were found to be only nonselective antagonists of histamine, acetylcholine and barium chloride and for this reason the attempts to find some stereoselectivity of action were rather hopeless; *cf.* the discussion in [400,401]. Morpholino derivatives **107** showed some diuretic activity [402].



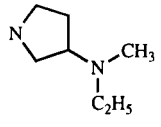
101, R = NH_2

102, R = $NHCH_3$

103, R = $N(CH_3)_2$

104, R = $NH(CH_2)_6COOH$

105, R =  , R^1 = H, R^2 = Cl

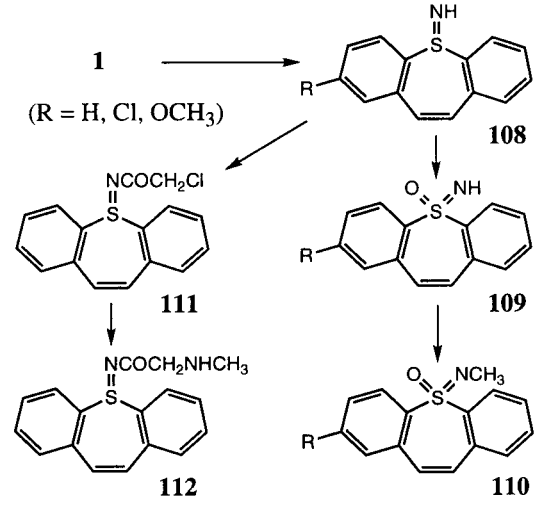
106, R =  , R^1 = H (Cl), R^2 = H

107, R =  , R^1 = Cl, R^2 = H

7. Sulfimides and Sulfoximides.

Ciba-Geigy [403] patented the synthesis of sulfimides **108** and **113** and of sulfoximides **109**, **110** and **114**. In their synthesis from dibenzo[*b,f*]thiepins **1** and dihydro derivatives **2**, the first step was the reaction with *O*-(mesitylenesulfonyl)hydroxylamine and the second oxidation with sodium periodate. The products were characterized as anticonvulsants (active towards pentetrazole convulsions) with mild sedative activity. Reaction of **108** (R = H) with chloroacetyl chloride gave **111** which was transformed (reaction with methylamine) to compound **112** [404], an antidepressant and central stimulant.

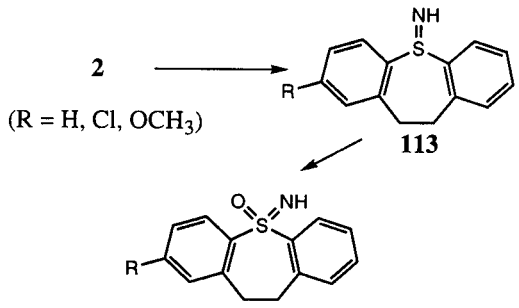
Scheme 14



8. Sulfones and Sulfoxides.

American Merck Sharp and Dohme together with the Canadian Merck Frosst devoted in 1977-1982 much experimental work to 3-functionalized dibenzo[*b,f*]thiepin

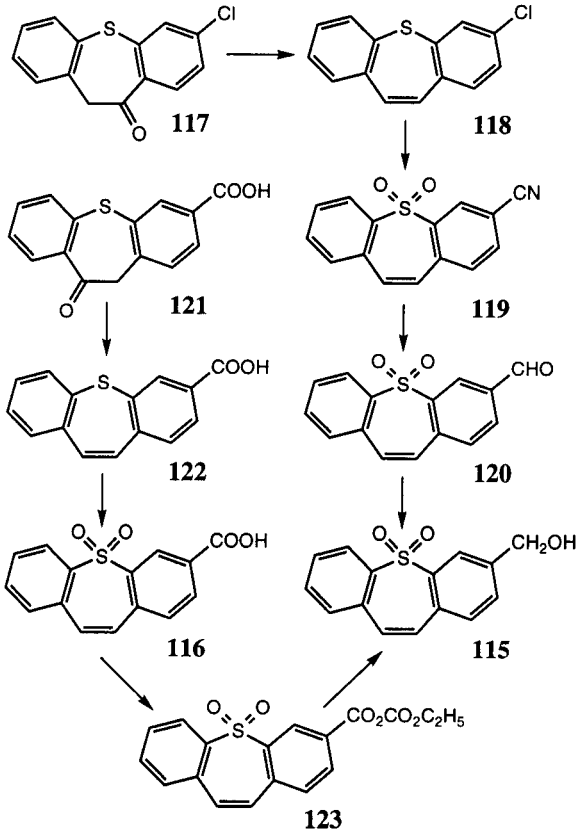
Scheme 15



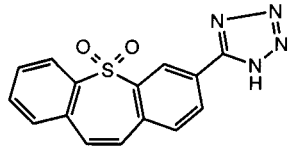
114

S,S-dioxides and *S*-oxides which were described as antagonists of the contractile prostanoids and of the thromboxane A2/endoperoxide receptor; they also inhibited platelet aggregation. They were thus expected to be potentially useful for treatment of asthma and thrombosis. The first of these compounds was the sulfone alcohol **L-640,035** (115) which was prepared using two synthetic routes [405,406]. The first started from the ketone **117** and proceeded *via* **118** (reduction and dehydration) and **119** (hydrogen peroxide, cuprous cyanide). The following step was the reduction with the Raney nickel alloy and formic acid to the aldehyde **120** which was reduced with sodium borohydride to the final product **115**. The second synthesis started from the oxo-acid **121** (obtained by cyclization of the corresponding di-acid) which was transformed *via* **122** to **116** (reduction, dehydration, hydrogen peroxide in acetic acid). The final two steps used the mixed anhydride **123** as the intermediate (ethyl chloroformate, sodium borohydride). Compound L-640,035 (**115**) was a clinical candidate which was subjected to preclinical investigation including pharmacology [407-410] and metabolic study [411]. The acid **116**, which was found to be the metabolite of **115**, was issued the code number **L-636,499**; it proved to have a similar activity profile [412].

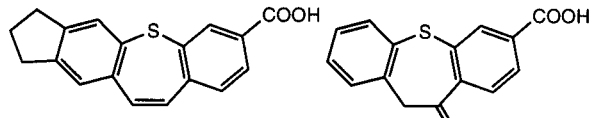
Scheme 16



The patented analogues, for which similar activity was claimed, were the following: aldehyde **120** [413], tetrazole **124** [414] being a bioisostere of L-636,499, and the sulfide acids **125** and **126** [415,416].



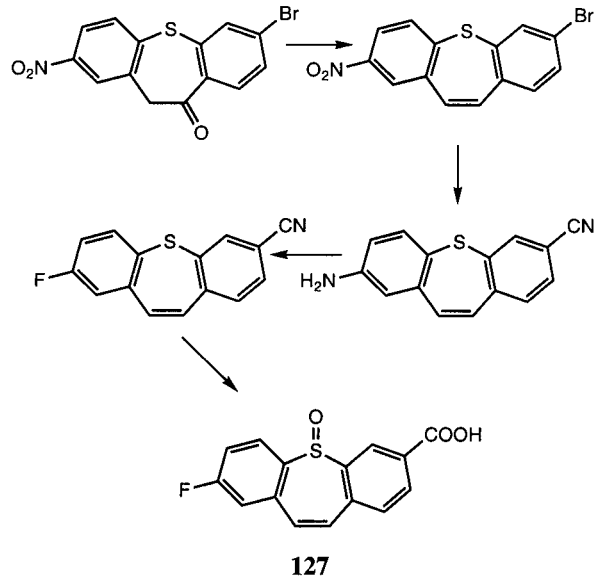
124



125 126

Further two compounds belonging to this series [417, 418] were two isomeric fluorinated 3-carboxysulfoxides **L-641,953 127** and compound **128** [419]. Their syntheses are shown in Schemes 17 and 18 and partly used methods just mentioned. For introduction of the fluorine atoms, heating of the corresponding diazonium fluoroborates was

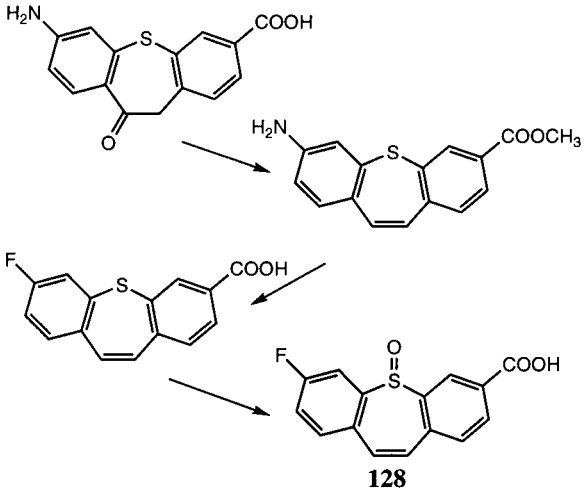
Scheme 17



127

used. Due to the presence of asymmetrically substituted sulfoxide groups, compounds **127** and **128** are chiral. Because of the great medicinal interest, a stereospecific sulfoxidation of the sulfide precursors of **127** and **128** [420] and three methods of resolution [419,421,422] of the racemic sulfoxides were elaborated. Stereoselectivity of the effects was proven.

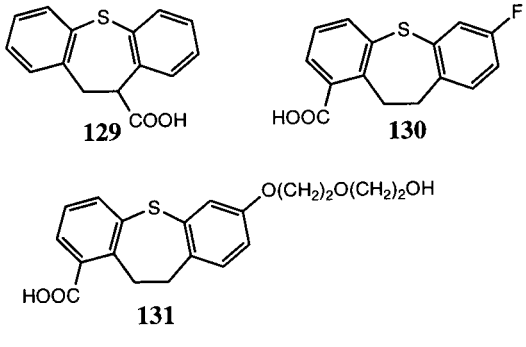
Scheme 18



128

9. Antiinflammatory Carboxylic Acids: Zaltoprofen.

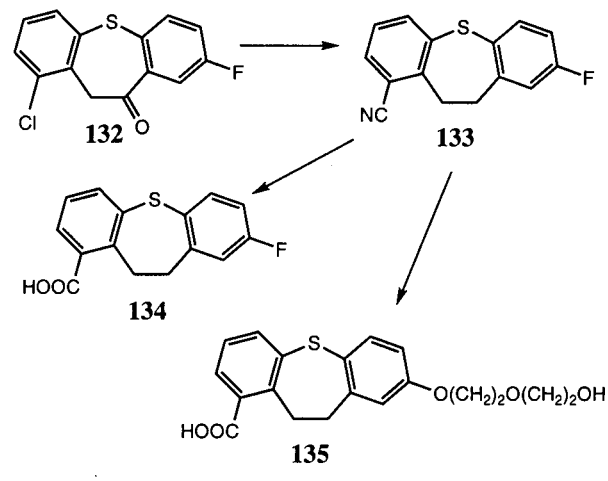
Much attention was paid to carboxylic acids of the dibenzo[*b,f*]thiepin series as potential antiinflammatory agents, especially by the Japanese companies Nippon Chemiphar and Dainippon, and the American Syntex. Even the most simple acid **129** (obtained by hydrolysis of the nitrile **22** [20]) showed this type of activity. 7-Substituted 10,11-dihydrodibenzo[*b,f*]thiepin-1-carboxylic acids **130** and **131** were patented as antiinflammatory agents by Japan Chemiphar Co. [423,424].



129 **130** **131**

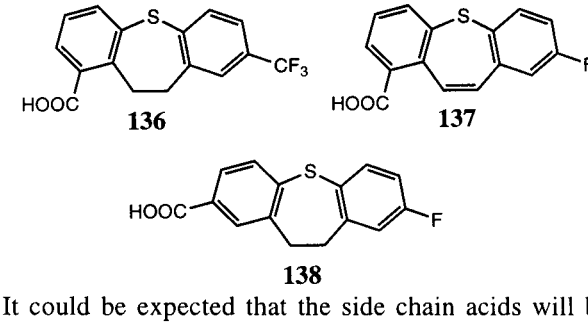
Similarly 8-substituted analogues **134** and **135** were prepared as shown in Scheme 19 [425-430]: The ketone **132** (obtained from the corresponding aromatic intermediate by cyclization) was transformed in two steps (cuprous cyanide and removal of the oxo group) to **133** which was hydrolyzed to the biologically active acid **134**. Hydrolysis of **133** with sodium hydroxide in diethylene glycol was accompanied by the exchange of the fluorine atom and led to the very active acid **135**.

Scheme 19



132 **133** **134** **135**

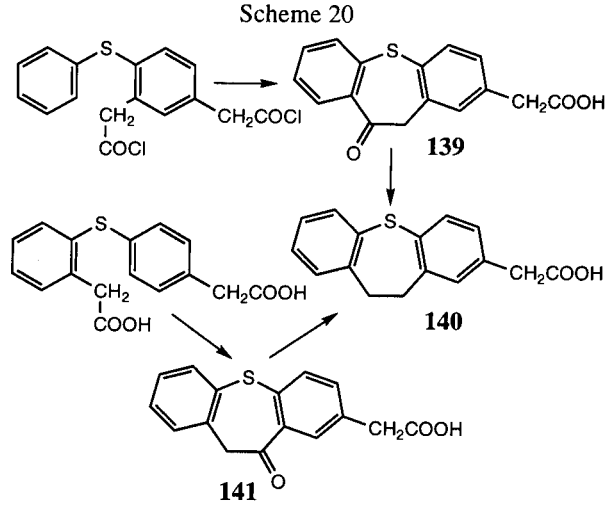
The acids **136-138**, prepared by similar methods, were protected by Nippon Chemiphar patents [431-433].



136 **137** **138**

It could be expected that the side chain acids will be more active than acids with carboxyl directly connected to the nucleus. Such acids - and **140** in the first line - were prepared simultaneously by Syntex [10,434] and Nippon Chemiphar [435,436]. Acid **140** was the most active prod-

Scheme 20

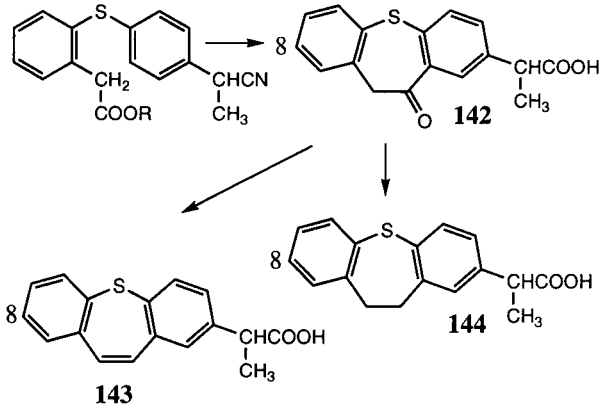


139 **140** **141**

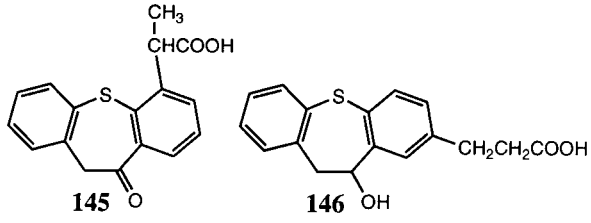
uct from the Syntex research [10]: 7 times more active than phenylbutazone in the rat paw assay (antiinflammatory effect) and 3 times more active than aspirin in the writhing assay in mice (nonopiate analgesic activity). It was prepared from the aromatic precursor *via* the acid **139** in three steps: cyclization, hydrolysis and removal of the oxo group by the Wolff-Kishner method (Huang-Min-lon modification). Nippon Chemiphar [435] used a slightly modified method proceeding *via* the isomeric **141**. This intermediate acid showed also activity higher than that of phenylbutazone [435,436].

The most favoured type are side chain propionic acids like **142-144** [437-440]. Their preparation from the same aromatic precursors is indicated in Scheme 21. Important activity was reported for derivatives of these acids substituted in position 8 with methyl [441-443], fluorine or methoxyl [444], hydroxyl [445], trifluoromethyl [446] and amino [447]. Further types of acids with antiinflammatory activity are represented by **145** [448] and **146** [449].

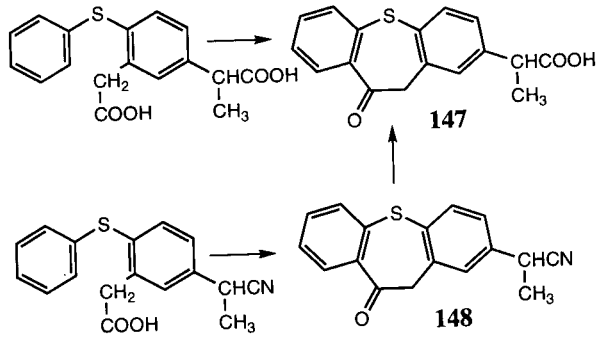
Scheme 21



The final product of this chapter is the acid **147**, called zaltoprofen, a product of Nippon Chemiphar. Its preparation by cyclization of the aromatic precursor [450] was described by making use of sulfuric acid [451] or polyphosphoric acid [452-456]. An alternative approach [457] proceeded *via* the nitrile **148**. Some patents described the purification of **147** [458,459], resolution of the racemic compound [460-462] and racemization of the inactive (*R*)(-)-enantiomer [463]. Zaltoprofen (**147**) was subjected to all phases of preclinical research: pharmacokinetics and metabolism [464-466], pharmacology [467-473] and toxicology [474-476]. Clinical studies were summarized in monographical articles [477-479]: it was found useful for treatment of chronic rheumatoid arthritis, arthrosis deformans, lumbago, postoperative, posttraumatic and postexodontic pain and was introduced into the market by Nippon Chemiphar in 1992 as Soretzon^R (tablets per 80 mg) and by Zeria in 1993 as Peon^R. The acid amide corresponding to zaltoprofen (**147**) was also stated to be an antiinflammatory and analgesic agent [480,481].

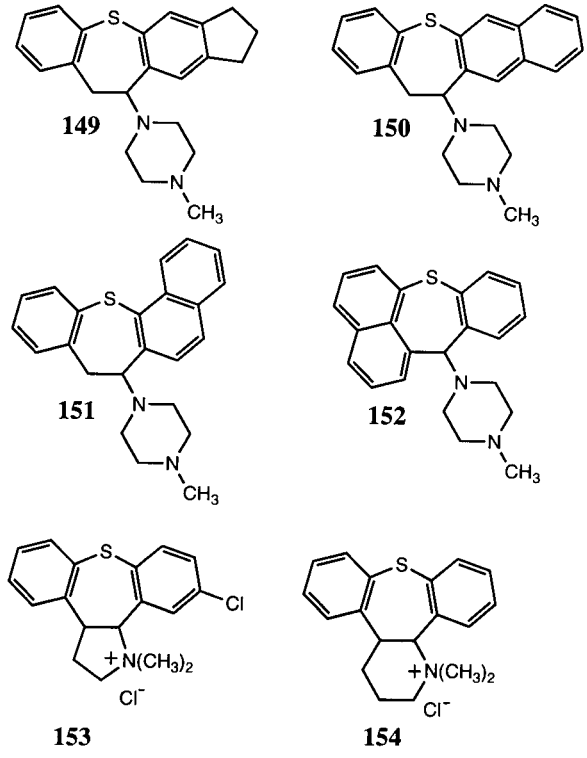


Scheme 22



10. Condensed Dibenzo[*b,f*]thiepins.

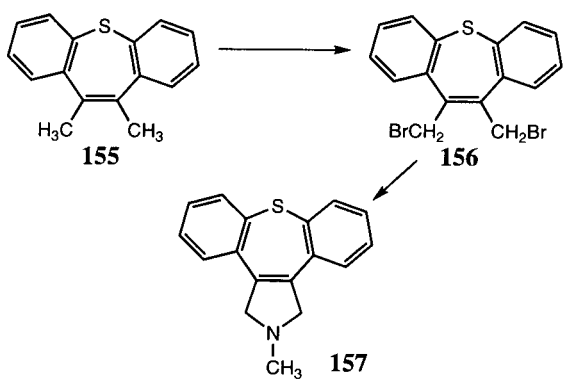
Condensed dibenzo[*b,f*]thiepins will be mentioned only in cases when the work had some medicinal background. Methylpiperazino derivatives of tetrahydro-7*H*-indeno-[5,6-*b*]-1-benzothiepin **149** [482], benzo[*b*]naphtho-

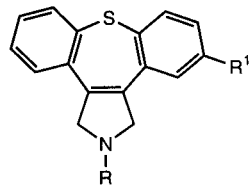


[2,3-*f*]thiepin **150** [483], benzo[*b*]naphtho[2,1-*f*]thiepin **151** [484] and benzo[*f*]naphtho[1,8-*bc*]thiepin **152** [485], prepared as analogues of perathiepin (**30**) *via* the corresponding ketones, proved to have only low CNS activity (tested as potential neuroleptics). The quaternary methochlorides of 11-chloro-1,1-dimethyl-2,3,3a,12b-tetrahydro-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*b*]pyrrolium (**153**) and cation 12-chloro-1,1-dimethyl-1,2,3,4,4a,13b-hexahydrodibenzo[2,3:6,7]thiepino[4,5-*b*]pyridinium cation (**154**) [13] were obtained from **16** and its lower side chain homologue by treatment with 1-methylpiperazine and found to be rather toxic and having antihistamine, anticholinergic and peripheral myorelaxant activities.

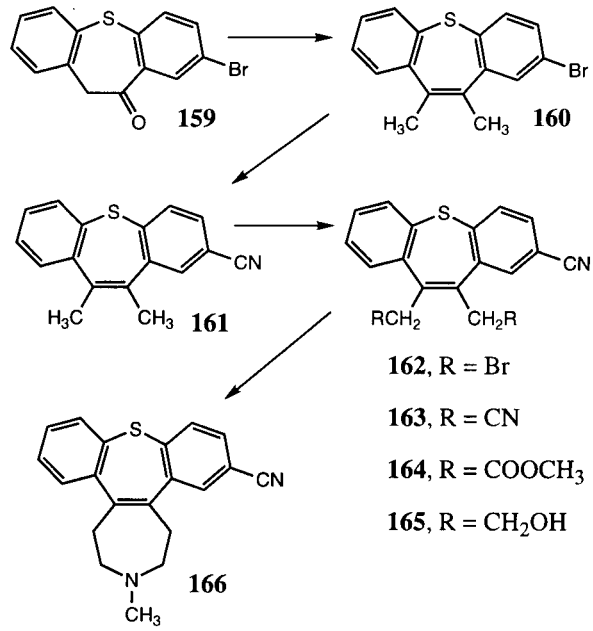
Ciba-Geigy developed a series of 2,3-dihydro-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*c*]pyrroles. The synthesis of the nuclearly unsubstituted member proceeded according to Scheme 23 [486]: The ketone **4** (R = H) was transformed in three steps (methylation, reaction with methylmagnesium iodide and dehydration) to compound **155** which was brominated with *N*-bromosuccinimide [487] to **156**. Treatment with methylamine gave the final product **157** which appeared under the code number GP 50302 as a potential neuroleptic agent. Pharmacological papers [488-490] described its profile including central anticholinergic and antiserotonin properties and characterized the intensity of its neuroleptic effects as being similar to those of chlorpromazine. In a pilot clinical trial, the agent failed to show therapeutic efficacy in acute schizophrenic patients but showed some therapeutic activity in depressed patients. It did not find practical use. Patents described analogues **158** with R being H and R^1 CH_3, Cl, Br, OCH_3, SCH_3, CF_3, CN, $CONH_2$ and OH [486, 491-496]. A more interesting compound was found in the bishomological series of 1,2,4,5-tetrahydro-1*H*-dibenzo-[2,3:6,7]thiepino[4,5-*d*]azepine. The selected compound was the 7-cyano-3-methyl derivative whose synthesis is shown in Scheme 24. The bromo ketone **159** was transformed similarly like in the foregoing case to compound **160**, **in which the bromine atom was exchanged with cyano by reaction** with cuprous cyanide. The nitrile **161** was processed in a routine way *via* **162-164** to the diol **165** whose ditosylate reacted with methylamine to give the neuroleptic citatepine (**166**) [497,498]. Its pharmacology was described in two papers [499,500]: typical neuroleptic but in all tests weaker than haloperidol; simultaneously, it showed strong α-adrenolytic, anticholinergic and medium antihistamine activity. Its introduction into the market seems unlikely.

Scheme 23





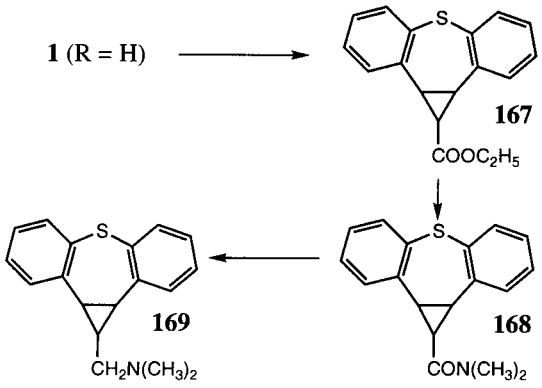
Scheme 24



1,1a,6,10b-Tetrahydrodibenzo[*b,f*]cyclopropa[*d*]thiepins, patented by Sumitomo Chemical Co. [501] were characterized as antidepressants with antireserpine effects and potentiating noradrenaline. The synthesis of a representative compound **169** is shown in Scheme 25: Dibenzo[*b,f*]-thiepin (**1**, R = H) was reacted with ethoxycarbonylcarbene, generated from ethyl diazoacetate, and the ester **167** was transformed *via* the dimethylamide **168** to the desired product **169**.

Lombardino (Pfizer) described [502,503] the synthesis of several 2-substituted 1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazoles **170** obtained by reactions of the diketone **6** (R = H) with aldehydes (or their protected forms) and

Scheme 25

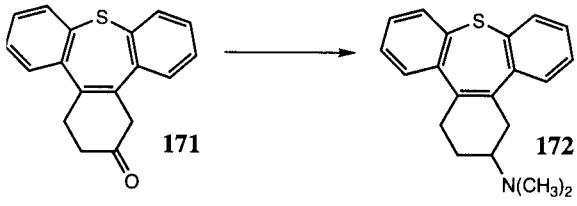


ammonium acetate in acetic acid. These compounds showed antiinflammatory activity in the test of carrageenan edema (rat foot) inhibition. Compounds **170** with R = CF_3 or 4-methoxyphenyl were the most active (but still less than phenylbutazone).

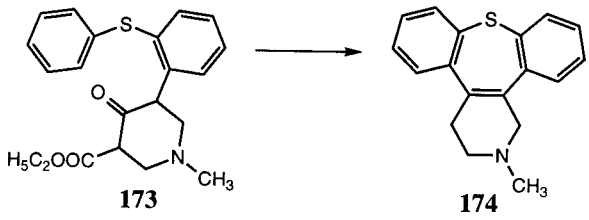
170

Organon (Akzo) first contributed CNS agents derived from 1,2,3,4-tetrahydrotribenzo[*b,d,f*]thiepin [504]. Reaction of the ketone **4** (R = H) with methyl vinyl ketone in ethanol (sodium ethoxide) resulted in the tetracyclic ketone **171** which was transformed by reductive amination with dimethylamine in a mixture of formic acid and formamide to the amine **172** (*cf.* Scheme 26). Antireserpine, antiaggressive and CNS depressant activities were given for this compound. The second contribution were 1,2,3,4-tetrahydrodibenzo[2,3:6,7]thiepino[4,5-*c*]pyridines with the 2-methyl derivative **174** as the selected compound [505]. It was prepared by heating the intermediate **173** (obtained evidently by Dieckmann cyclization of the corresponding precursor) with polyphosphoric acid (Scheme 27). The compound was characterized as an antidepressant. Its *trans*-dibydro derivative **177** [506] was synthesized from ethyl 3-(methylamino)propionate which was acylated with 2-(2-phenylthiophenyl)acetyl chloride

Scheme 26

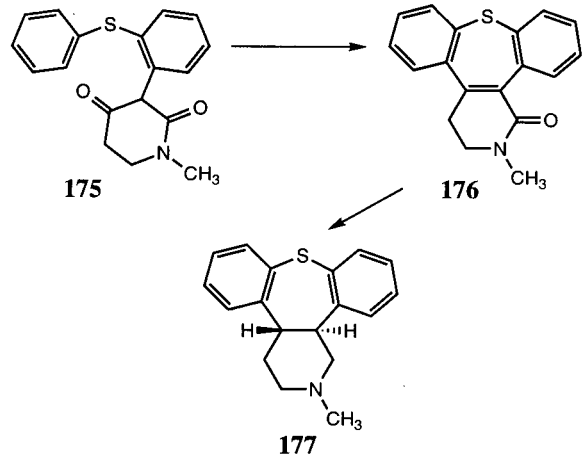


Scheme 27



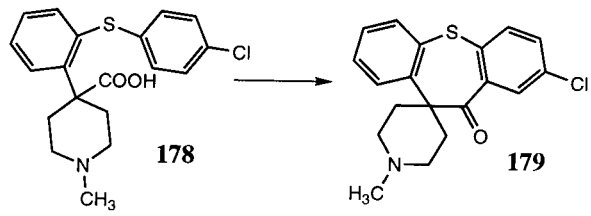
and the product was cyclized with potassium *tert*-butoxide in toluene to **175**. Polyphosphoric acid effected cyclization to **176** which was reduced in two steps (magnesium in methanol and then lithium aluminium hydride) (Scheme 28) to the product **177 for which CNS depressant activity was demonstrated.** The compound was included into a QSAR study [507] considering a series of neurotropic effects.

Scheme 28



The American Hoechst patented [508] the spirocyclic piperidine **179** obtained by cyclization of the amino acid **178** by heating with phosphoryl chloride. Analgesic, tranquilizing and anticonvulsant effects were given for the product.

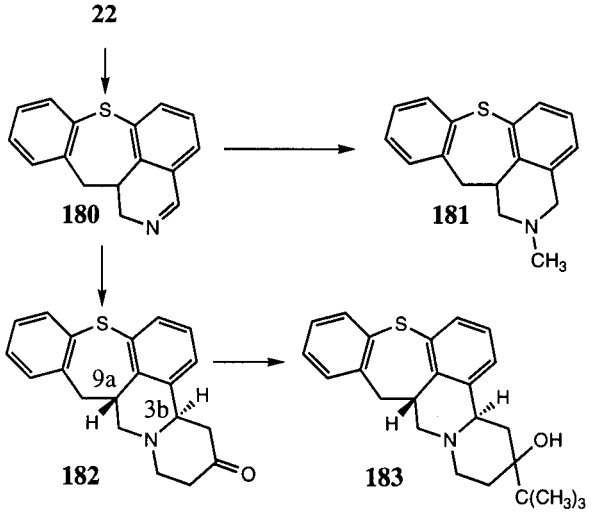
Scheme 29



The last compound which should be mentioned is "thiaisobutaclamol" (**183**) which was prepared by Šindelář in the Prague laboratory [509] by a multistep synthesis (Scheme 30). The nitrile **22** was transformed by reduction

and formylation to the formamidomethyl compound which was cyclized by the Bischler-Napieralski reaction to **180**. Reduction of this compound and *N*-methylation led to 2-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzothiepino[2,3,4-*ed*]isoquinoline (**181**) eliciting antireserpine effects (potential antidepressant). Addition of **180** to methyl vinyl ketone gave the pentacyclic ketone **182** with fixed configuration at C-3b and C-9a. Reaction with *tert*-butylmagnesium chloride produced in a low yield **183** as a mixture of stereoisomers which displayed high affinity to dopamine receptors in the striatum of the rat brain confirming thus the neuroleptic character of the product.

Scheme 30



11. Conclusion.

The purpose of this review was not only to summarize the distribution of various biological activities in the structural field of dibenzo[*b,f*]thiepin derivatives but also to state that the dibenzo[*b,f*]thiepin system appears as a fruitful carrier system for further new drug discovery investigations.

12. REFERENCES AND NOTES [c]

[a] Short version of this review was given as a plenary lecture at the Symposium on Heterocyclic Compounds: Synthesis, Structure and Biological Activity, Hradec Králové, Czech Republic, June 28, 1995.

[b] Address for correspondence: Dr. Miroslav Protiva, Post Office 31, Slezská 107, 130 01 Prague 3, Czech Republic.

[c] The recently introduced following symbols for patent documents (patents and applications) are used instead of those used in Chemical Abstracts (in parentheses): AT (Austrian), BE (Belgium), BR (Brazil Pedido PI), CA (Canada), CH (Swiss), CS (Czechoslovakia), DE (German including German Offen.), EP (European Pat. Appl.), FR (French including French Demande), GB (British including British UK Patent Appl.), JP (Japan including Japan Kokai Tokkyo Koho), NL (Netherlands including Netherlands Appl.), US (U.S.) and ZA (South African). Differentiation of patents and applications is clear from the Chemical Abstracts references which are given in all cases of patent documents.

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