BIOLOGICALLY ACTIVE HETEROCYCLIC ANALOGS OF THIOUREA (REVIEW)

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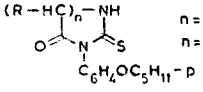
The results of research carried out in the Scientific-Research Institute of Medicinals (Budapest, Hungary) are correlated. The structures of 2-aminothiazolines, which can exist in the tautomeric 2-iminothiazolidine form, and of the corresponding analogs of the thiazine series and their acyl derivatives are discussed. A new method for the synthesis of 3-aryl-substituted 2-iminothiazolidines and 2-iminoperhydro-1,3-thiazines is examined. Data on the biological activity of some of the investigated compounds are presented.

The enormous amount of research devoted to the study of the biological activity of thiourea and its cyclic analogs make it impossible to give an exhaustive review of the studies in this area within the framework of the present paper. Of the advances made in recent years, one should mention the discovery of the vascular activity of 2-(2,6-dimethylphenylimino)thiazolidine [2] and the many-sided biological activity of its thiazine analogs [3-5]. The latter compound has found application as an analgetic in veterinary medicine under the name Rompun (Bayer A.-G.).

At the beginning of our studies in 1964 the amount of research that had been devoted to the study of the biological activity of compounds containing the thiourea skeleton in their molecules was quite inadequate. We hoped that derivatives of this type would prove to be bioisosteric with the biologically active derivatives of urea or guanidine.*

It must be noted that the interest in the pharmaceutical chemistry of compounds containing the thiourea skeleton has not waned in the last decade. For example, new antihypertensive preparations based on 1-aryl- and 1-aryl-3-alkylthioureas [9, 10], as well as antiphlogistic preparations in the 1-aryl-3-(hydroxyethyl)-thiourea series [11], have been described. Of the cyclic analogs, one must mention 2-arylimino-3-alkylthiazolidines, which have antiectoparasitic properties [12], and 2-arylimino-substituted thiazolidines and perhydrothiazines [13], and analogs of the antihypertensive preparation klonidin [2,6-dichlorophenyliminoimidazolidine (Catapresan)].

Our first studies involved a search for antituberculous preparations structurally similar to Isoxyl [bis-(4-isoamyloxyphenyl)thiourea] [14], which is not always effective, possibly because of poor absorption. The corresponding thiohydantoins were synthesized from 4-isoamyloxyphenyl isothiocyanate through the thiocarbamoyl-α-amino acid, and the analogous six- and seven-membered heterocyclic compounds were synthesized from β- and γ-amino acids [15-17].



n = 1; R = H, substituent in the amino-acid residue
n = 2, 3; R = H

The synthesized thiohydantoins displayed in vitro activity (their six- and seven-membered analogs were not active) but were found to be toxic in experiments with mice.

* For example, it is known that 2-(octahydro-1-azocinyl)ethylguanidine (guanethidine) has excellent antihypertensive properties [6-8].

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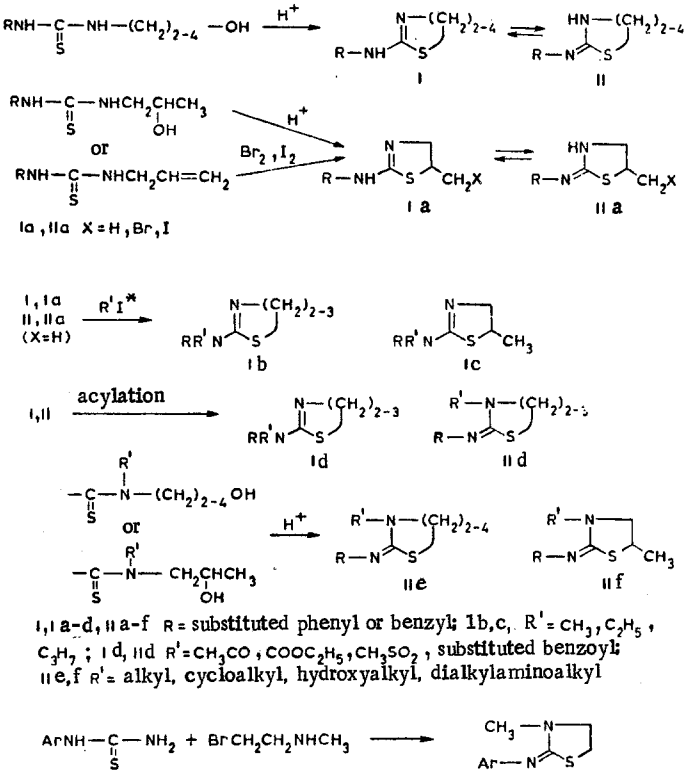
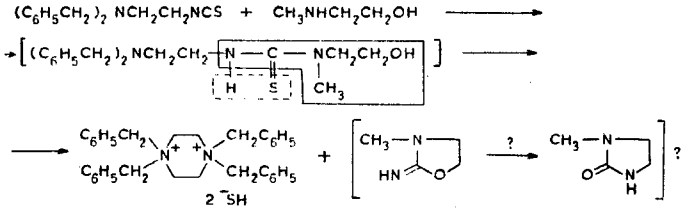
Synthesis of 2-Substituted 2-Aminothiazolines and Their Analogs

One of the trends in our studies was the synthesis of 2-amino-substituted heterocycles from thiourea derivatives:



Methods similar to those described in the literature [1] were used for the synthesis of the starting thiourea derivatives. Their cyclization and subsequent alkylation or acylation were also accomplished in analogy with the literature data [3, 18-20]. Thiazepines of the I ⇌ II and IIe type were also obtained from substituted (4-hydroxybutyl)thioureas by cyclization in acidic media [21], although according to the data in [22], this reaction does not lead to the expected results.

The results of the research as a whole have been the subject of two correlations [23, 24]. The synthesis of the starting thioureas has been described in patents [25, 26]; the synthesis of I, Ia, II, IIa [27], Ib and Ic [28-30], Id and IId [31-33], and IIe and IIh [28-30, 34-36] has also been described. At this point two interesting features of these synthetic studies [37, 38] can be noted. A diquaternary piperazinium salt, which is probably formed as a result of decomposition of the intermediate thiourea derivative, was obtained when a solution of 2-dibenzylaminoethyl isothiocyanate and aminoethanol in benzene was refluxed. It might have been expected that cyclization of the simultaneously formed cyanamide would lead to a 2-iminooxazolidine or 2-imidazolidone; however, these compounds could not be isolated.



The chlorination of 2-arylimino-3-(hydroxyethyl)thiazolidines with thionyl chloride also led to interesting results; 7-aryl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazolium salts were obtained in this case. The fluorination of the above-indicated thiazolidines with the Yarovenko reagent [trifluorochlorotriethylamine (fluoramine)] leads to the same salts. The synthesis of these thiazolium salts by a different method was previously described [39, 40]:

* A small amount of a 3-alkyl derivative of the II type (IIb or IIc) is formed in some cases.

Structure of 2-Arylaminothiazolidines (2-aryliminothiazolidines) and Their Six- and Seven-Membered Analogs

The structures of thiazolines, thiazines, and thiazepines, which can exist in two tautomeric forms I and II when R = H, and of their acyl derivatives, which have structure I or II (R = acetyl, carbethoxy, benzoyl, and mesyl), have been studied by many research groups (the structures of the acylated derivatives have been studied primarily by our group):

I II

However, up until most recently the results of these studies have not been free of contradictions. The chief reason for the contradictions is the fact that primarily the spectral characteristics of the corresponding compounds have been examined. Since these spectral characteristics are also associated with the nature of the substituents in the ring, the ring size, the conformational peculiarities of the molecule, and, in the NMR spectra, with the anisotropic effects of the substituents, the differences in them that are due precisely to structural isomerism can hardly always be revealed.

The use of model derivatives of the I and II type (usually R = CH_3) or the isolation of two isomeric acylation products of the I and II type does not aid in overcoming these difficulties.

We will not consider here those studies in which UV spectroscopy was used to solve the structural problems [20, 28, 41-43], since they were later subjected to criticism. It was later found that mass spectrometry [24, 44] was also unsuitable for the solution of this problem.

Data obtained by means of IR and NMR spectroscopy for the bases of this series and their N-acyl derivatives will be correlated below. Only one isomer was obtained in the acetylation and benzoylation of the bases; in some cases two isomers were obtained as a result of introduction of carbethoxy groups, whereas the isomer (in the individual state or containing only a small amount of the second isomer) that could be thermally converted to the other isomer was obtained in the case of mesylation [31-33]. The ionic mechanism of this migration of the mesyl grouping was confirmed in [45-47].

The structures of thiazone derivatives were first studied by IR spectroscopy by Najer and co-workers [20]. By examining the $\nu_{C=N}$ frequencies and using model compounds they were able to express the opinion that compounds of this type exist in 2-phenylaminothiazine tautomeric form I. Engoyan and co-workers [43] later arrived at the same conclusion.

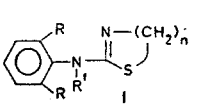
In the course of our studies we obtained phenylamino-substituted thiazolines and thiazones labeled with ^{15}N in both the endo and exo positions and compared the ν_{NH} and $\nu_{C=N}$ frequencies for the labeled and unlabeled compounds (solutions in chloroform). The results obtained in the case of the thiazine derivative were in exact agreement with the values calculated from Hooke's law (with allowance for the character of the group vibrations) of the frequencies for tautomeric structure II, whereas only a small difference in the frequencies of the corresponding tautomeric structures was noted in the case of thiazoline [48].

In this connection, we undertook a study of the $\nu_{C=N}$ frequencies of a large number of compounds in order to ascertain how characteristic the $\sim 30\text{-cm}^{-1}$ decrease in the case of isomers II, as compared with isomers I, is [49].

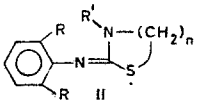
Examination of the data for model compounds with a fixed structure or with a structure established by other methods makes it possible to note that the $\nu_{C=N}$ values are unsuitable for establishment of the position of the double bond in these molecules (Table 1). For example, it is apparent from a comparison of the model pairs 4-5 and 10-11 that the directions of the shift of the $\nu_{C=N}$ frequencies are just the opposite; the frequencies for the pair of isomeric mesylamides 29-30 do not differ, and the difference for the 20-21 pair is very low, although for isomeric thiazepines with analogous structures this difference may be extremely large. It is thus evident that the position of the $\nu_{C=N}$ bands changes ambiguously as the structure changes.

Cherbuliez [50] and Rabinovitz [51] were the first to use PMR spectroscopy for the identification of structures of the I and II type. It might be expected that the chemical shift of the protons of the methylene group in

TABLE 1. Spectral Characteristics of 2-Aminothiazolines, 2-Iminothiazolidines, and Their Analogs



I



II

Compound	R	R'	n	$\nu_{C=N}$[a], cm^{-1}	^{1}H NMR[b] δ, ppm NCH$_2$ (t)	^{1}H NMR[b] δ, ppm CCH$_2$ (m)	proposed structure	^{13}C NMR[c] δ, ppm C_{para}	^{13}C NMR[c] δ, ppm $C_{(5)}$	proved structure
1	CH_3	H	2	1655	3,70		I	123,7		II[d]
2	CH_3, 3-NO_2	H	2	1640	3,30		?			
3	2-C_6H_5, 6-Br, 3-Br	H	2	1640	3,20		?			
4[e]	CH_3	CH_3	2	1620	4,15		I	128,1		I
5[e]	CH_3	CH_3	2	1630	3,36		II	122,6		II
6[f]	CH_3	H	3	1625	3,35	1,90	II	122,7		II[d]
7[e]	CH_3	CH_3	3	1613	3,70	1,78	I			I
8[e]	CH_3	CH_3	3	1605	3,37	2,12	II			II
9	Cl	H	2	1645	3,70		I	125,3		II
10[e]	Cl	CH_3	2	1621	4,17		I	129,6		I
11[e]	Cl	CH_3	2	1630	3,60		II	123,6		II
12	Cl	H	3	1625	3,40	1,95	II	124,7	24,5	II
13[e]	Cl	CH_3	3	1625	3,70	1,80	I			I
14[e]	Cl	CH_3	3	1590	3,43	2,15	II			II
15	CH_3	CH_3CO	2	1650	4,35		I	123,9		II
16	CH_3	CH_3CO	3	1635	3,95	2,10	I	124,0		II
17	CH_3	$COOC_2H_5$	2	1650	4,20		I	123,5		II
18	CH_3	$COOC_2H_5$	3	1630	4,00		I	123,9	23,1	II
19	Cl	$COOC_2H_5$	2	1630	4,30		I	124,5		II
20	Cl	$COOC_2H_5$	3	1630	3,60	1,80	II	129,0	20,2	I
21	Cl	$COOC_2H_5$	3	1620	3,90	2,10	I	124,7	23,0	II
22	CH_3	C_6H_5CO	2		4,25		I	123,5		II
23	CH_3	C_6H_5CO	3		4,00		I	123,9	24,3	II[d]
24	CH_3	o-$CH_3C_6H_4CO$	2		4,30		I→II	123,4		II
25	CH_3	o-$CH_3C_6H_4CO$	3		4,05		I→II	123,7	24,1	II
26	CH_3	o-ClC_6H_4CO	3		4,15		I→II	123,8	23,7	II
27	CH_3	CH_3SO_2	2	1620	4,15		II ↓	129,8		I[d] ↓
28	CH_3	CH_3SO_2	2	1640	4,30		I	124,0		II[d]
29	CH_3	CH_3SO_2	3	1630	3,90		II ↓	129,5	19,1	I[d] ↓
30	CH_3	CH_3SO_2	3	1630	3,90		I	123,7	24,7	II[d]
31	Cl	H	4	1610	3,42		II	123,1		II
32[e]	Cl	CH_3	4	1580	3,61		II	122,6		II

[a]In KBr pellets. [b]With a JEOL 60-HL spectrometer and solutions in $CDCl_3$. [c]With a Varian XL-100 spectrometer and solutions in $CDCl_3$ or d_6-DMSO. [d]The structure was also confirmed by x-ray diffraction. [e]This is a model compound with unambiguous structure. [f]This compound was also investigated by Jackman and Jen [42].

the 4 position of the heteroring (δ_{NCH_2}) would be higher for isomer I than for compounds of the II type because of the large −I effect of the sp^2 nitrogen atom. In fact, it was found that the regularity δ_{NCH_2} (I) > δ_{NCH_2} (II) is followed very distinctly for pairs of model compounds 4-5, 7-8, 10-11, and 13-14 and that this difference may serve as a basis for the identification of the tautomeric or isomeric structures of other compounds (Table 1) [29].

We used this method to assign tautomeric structure I to thiazoline derivatives and structure II to thiazine derivatives [27], structures II-I to isomeric carbethoxy derivatives 20-21 [31], and structures II-I to isomeric mesylamides 27-28 with simultaneous establishment of the direction of migration of the mesyl group (II → I) [33]. In the case of those acetyl, carbethoxy, and benzoyl derivatives for which only one isomer could be isolated structure I could be assigned with high probability with allowance for the relatively high δ_{NCH_2} values [32, 33].

However, we cannot fail to point out certain anomalies. For example, as the ring size changes the difference in the chemical shifts for isomers of the same type may change to a greater degree than on passing from one isomer to another with the same ring size (compare 19-21 and 20-21). The δ_{NCH_2} values are identical for the isomeric mesylamides 29-30, whereas the δ_{NCH_2} difference is very small for 27-28, and a very small δ_{NCH_2} value for thiazolines 2 and 3, which indicates structure II, is also evident. All of these results constitute evidence for the inadequacy of the PMR method, the general reason for which is the strong effect of the anisotropy of the substituents on the chemical shift of the protons of the methylene group. In addition, one

must take into account the fact that in the case of acyl derivatives the sp^2 nitrogen atom in the isomer of the II type is replaced by an amide nitrogen atom, which is also an electron-deficient atom and therefore acts as a substituent with a −I effect.

A new method developed in our institute and involving the different effect of solvents (chloroform and trifluoroacetic acid) on the shift of the protons of the heteroring also led to further contradictions. The method, which is based on the difference in δ_{NCH_2} and δ_{SCH_2} in these solvents, confirms the previously determined structures of some acetamides, mesylamides, and benzamides but also indicates alternative structures for o-substituted benzamides (Table 1, compounds 24-26 and the o-chlorobenzamide analog of compound 24), and structure II was therefore assigned to these compounds [52-54].

To solve this problem we used x-ray-diffraction analysis, which confirmed structure II of the benzamides [55-57].

With allowance for all of the results it is clear that the δ_{NCH_2} shifts are unsuitable for the determination of the structures. Engoyan and co-workers [43] recently arrived at the same conclusion; however, they feel that it is possible to use the position of the signal of the 5-CH_2 (CCH_2) group for the determination of the structure. Although in the course of our studies for model compounds 7-8 and 13-14 we noted an appreciable difference in δ_{CCH_2} [δ_{CCH_2} (II) > δ_{CCH_2} (I)] whereas the δ_{CCH_2} signal of thiazine 6 differed only slightly (~ 0.1 ppm) with respect to its position from the signal of model compound 7 with structure I [23] (see also the extremely similar data for thiazine 12), on the whole we were unable to use this insubstantial difference as a basis for the determination of the structures.

However, Engoyan and co-workers in a study of a large number of model compounds expressed the opinion that 2-arylamino-5,6-dihydro-4H-1,3-thiazine derivatives exist in tautomeric form I.*

Since it was found that the chemical shifts of the protons of the heteroring can be used for the determination of tautomeric structures only with great caution, we decided to ascertain how suitable the expected difference in the electron-density distribution in the aromatic rings of isomeric structures I and II is for the solution of this problem. It was established that the multiplets of the aromatic protons in the PMR spectra of the isomeric 5-6, 7-8, 10-11, and 12-13 pairs have characteristic differences that do not depend on the size of the heteroring [29]. Since this effect is associated with an increase in the electron density in the ortho and para positions of the aromatic ring in isomer II as a consequence of an increase in conjugation, it seemed expedient to again turn to the solution of this problem by means of ^{13}C NMR spectroscopy.

This method was used by Jackman and Jen to prove the structure of various tautomeric cyclic amidines, guanidines, and related compounds, including two 2-arylaminothiazines [42] [compound 6 (Table 1) and its phenyl analog]. During a study of two isomeric N-methyl-substituted 2-phenylaminothiazines as model compounds it was shown that in the spectrum of isomer I the chemical shift of the carbon atom in the para position of the aromatic ring is the same as in the spectrum of benzene (δ 128 ppm), whereas in the spectrum of isomer II it decreases to 123 ppm. The same value was found for the two investigated thiazines, and this confirms their tautomeric structure (II).

Although this result was in agreement with the results of PMR studies [27, 50, 51], we decided to again verify the structures of some characteristic representatives of various types of compounds that we had previously investigated by means of ^{13}C NMR spectroscopy [58]. In some cases we also used x-ray-diffraction analysis as a control method [59]. The latter method confirmed a structure of the II type for thiazine 6.

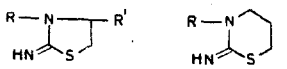
It is apparent from Table 1 that thiazolines also exist in tautomeric form II. All of the acetyl and benzoyl derivatives have the same II structure, so that in some cases the previously assigned I structure must be rejected. A similar situation also arises for carbethoxy isomers 20-21, as well as for isomeric mesylamides 27-28 and 29-30. The direction of migration of the mesyl grouping (I → II) should also be simultaneously corrected. The structure of thiazepine 31 corresponds to the previously established II structure.

In conclusion, it can be stated that not only inductive but also anisotropic effects of substituents influence the position of the signals in the PMR spectra of the investigated types of compounds; the effects are so strong that in a number of cases the chemical shifts cannot be unambiguously related to the tautomeric I and II structures. Only ^{13}C NMR spectroscopy supplemented by the results of x-ray-diffraction analysis gives reliable results. Both of these methods indicate the higher stability of structures of the II type.

* It must be noted that conclusions of this sort cannot be drawn from simular data published by Jackman and Jen [42], since the position of the δ_{CCH_2} signal of 2-phenylaminothiazine differs identically from the position of the corresponding signals of the isomeric N-methyl derivatives (0.17 and 0.18 ppm).

Synthesis of 3-Substituted 2-Iminothiazolidines and 2-Iminoperhydrothiazines

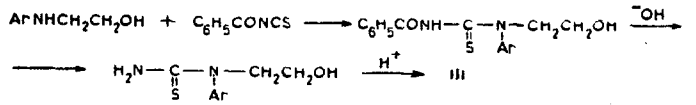
Within the framework of our study of the problem of the interrelationship between the structure and physiological activity, it seemed of interest to synthesize 3-substituted 2-iminothiazolidines and their six-membered analogs, which are isomers of the previously investigated heterocycles:



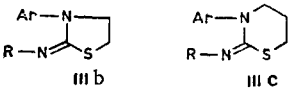
III IIIa

R — substituted phenyl and some other groups, R′=H, CH_3, CH_2OH

Thiazolidines III could be synthesized by a known method from N-arylethyleneimines and thioureas [60], but the starting compounds with the appropriate structures necessary for this are difficult to obtain. For the same reason we obtained only a few compounds by means of another known method for the synthesis of thiazolidines based on cyclization of 1,3-disubstituted 1-(hydroxyethyl)thioureas to substituted imino derivatives IIIb in acidic media [61], although this reaction has been investigated more extensively for 3-unsubstituted thioureas [62].



In our search for a general method for the synthesis of compounds of this type that would also be suitable for the preparation of the still unknown thiazines IIIa, we turned to a previously described method based on the reaction of 3-substituted 1-arylthioureas with dihalo derivatives [41, 61, 63-67]. In this case one might have expected the formation of substituted (at the exocyclic nitrogen atom) iminothiazolidines IIIb or iminoperhydro-1,3-thiazines IIIc.

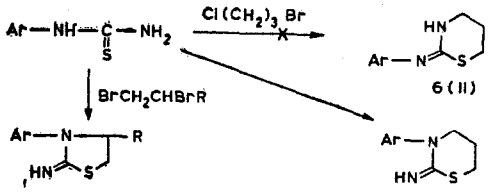


IIIb IIIc

R = aryl, aralkyl, alkyl

However, the literature data indicated the inapplicability of this method to monoarylthioureas, since in this case ethylenebis(isothiuronium) salts rather than 2-imino-3-arylthiazolidines are formed in the reaction with 1,2-dibromoethane [61, 64]. A similar reaction with other dihaloalkanes has also been reported [68], although in the opinion expressed in [3], the reaction of 1-arylthioureas with 1,3-dihalopropanes leads to 2-aryliminoperhydro-1,3-thiazines. During a verification of this reaction in the example indicated below it was established that the product in this case does not have the 2-arylimino derivative structure 6 as indicated in [3] but rather is 3-aryl-substituted perhydrothiazine 33.* The reaction of many other 1-arylthioureas with 1,3-dihalopropane also led to the same result. After this, by using a large excess of the corresponding 1,2-dihalo compounds we were able to synthesize 2-iminothiazolidines of the 34 type [69, 70].

The weak and very narrow ν_{NH} band in the IR spectra of compounds of the III and IIIa type differs markedly from the intense and diffuse ν_{NH} band in the spectra of heterocycles of the I and II type. A dependence of the δ_{NCH_2} chemical shift on the number of atoms in the heteroring is observed in the PMR spectra of these compounds [23].



Ar = 2,6-dimethylphenyl, R = H, CH_3, CH_2OH

34 (R=H, III);	33 (IIIa)
ν_{NH} 3270 cm^{-1} (KBr);	3305 cm^{-1}
δ_{NCH_2} ($CDCl_3$) 3,85 ppm;	3,55 ppm

* It must be noted that similar results were also obtained by others for a number of naphthyl derivatives [71].

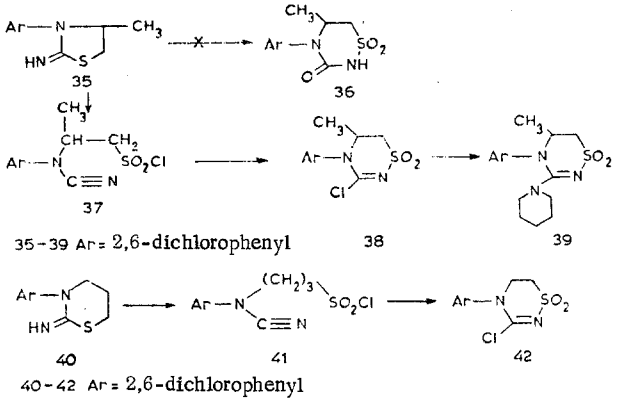
TABLE 2. Principal Absorption Bands (cm^{-1}) in the IR Spectra of Cyanamides 37 and 38 and Cyclic Sulfonylformamidines 41 and 42*

Compound	$\nu_{C\equiv N}$	$\nu_{C=N}$	$\nu_{SO_2}^{as}$	$\nu_{SO_2}^{s}$	δ_{SO_2}
37	2230	—	1375	1170	570, 530
38	—	1600	1350, 1320	1180, 1155	570
41	2220	—	1370	1180	600, 530
42	—	1615	1340, 1320	1180, 1150	571

* Spectra were obtained from KBr pellets.

The structures of III and IIIa were proved unambiguously (in addition to the fact that iminothiazolidine 34 was also synthesized by a different method [61]) by oxidative reactions [69], which were accomplished by means of potassium chlorate in hydrochloric acid under conditions similar to the literature conditions for thiazolidines of the IIIb type [63, 64, 72]. However, in this case oxidation led to different reaction products. Thus, instead of the expected oxothiadiazine derivative 36, compound 35 initially gives cyano compound 37, which undergoes thermal cyclization to chlorothiadiazine derivative 38. Compounds of the latter type react readily with amines to give cyclic sulfaguanidines (for example, compound 39).

Perhydrothiazines are similarly oxidized, but we observed subsequent cyclization of the resulting cyano compounds in only one case:



The 37 → 38 and 41 → 42 conversions illustrate a new type of addition of a sulfonyl chloride to the cyanamide grouping, regarding which only negative results had been presented in the literature up to this time [73].

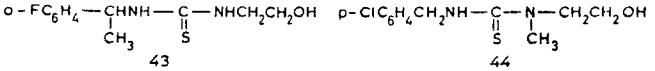
Compounds 38 and 42 constitute a new type of cyclic sulfonylformamidine, and compound 42 is a new type of 1,2,4-thiadiazepine.

The structures of the oxidation products were confirmed by their IR spectra (Table 2).

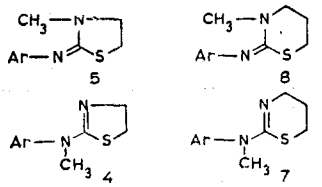
The absence of ν_{NH}, ν_{OH}, and $\nu_{C=O}$ bands also corresponds to the proposed structures. The splitting of the ν_{SO_2} band is due to the conjugation of the C=N bond [74].

Biological Activity of 2-Iminothiazolidines, 2-Aminothiazolines, and Their Six-Membered Analogs

Many of the compounds described in this review have displayed diverse types of biological activity. In particular, hydroxyalkylthioureas, which are used as starting compounds in the synthesis of heterocycles, were active. For example, strong diuretic activity is characteristic for compound 43, whereas hypotensive activity is characteristic for compound 44.



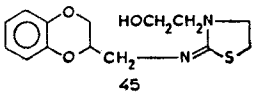
Of the heterocyclic derivatives, 2-imino-substituted heterocycles were particularly biologically active.



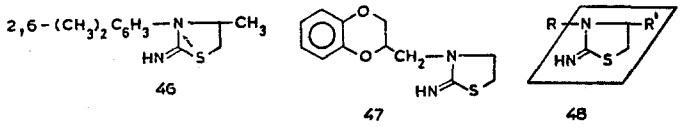
Ar = 2,6-dimethylphenyl

Compounds 5 and 8 have displayed diuretic activity similar to the activity of dihydrochlorothiazide with sedative-hypnotic character. A sedative-hypnotic effect was the principal effect for isomeric compounds 4 and 7.

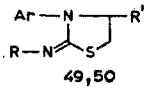
Compound 45, which increases the activity of the centers that transmit stimuli to the brain by means of noradrenaline, was of interest.



Iminothiazolidines 46 and 47 display antihypertensive properties, and their activity is approximately an order of magnitude higher than the activity of guanethidine. Thus we observed a new type of prosthetic grouping (compound 48) with antihypertensive activity.



Unfortunately, these compounds also had neurotoxic activity of the strychnine type. However, this fact directed our attention to a study of the CNS activity of iminothiazolidines. Compounds 49 and 50, which are capable of shielding muscular relaxation induced by CNS depressants and intensifying the polysynaptic reflexes of the spinal chord, are most interesting from this point of view. Thus this group of compounds constitutes a new type of CNS stimulator.



49 R,R' = CH_3, Ar = 2,6-dichlorophenyl
50 R = H, Ar = 2,6-dichlorophenyl R' = CH_2OH

All of these results show that heterocyclic compounds with a thiourea skeleton are interesting subjects for pharmacological studies.

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SYNTHESIS OF N-HETEROAROMATIC ONIUM BETAINES OF INDANE-1,3-DIONE

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UDC 547.665

Betaines are formed in good yields in the reaction of N-heteroaromatic compounds with 2-dicyanomethyleneindane-1,3-dione oxide and its 4- and 5-halo derivatives in dioxane. The corresponding oxides were obtained by oxidation of 2-dicyanomethyleneindane-1,3-dione and its 4- and 5-substituted derivatives with hydrogen peroxide in dioxane. Data from the IR spectra of the compounds are presented.

Onium betaines in the indane-1,3-dione series were discovered recently. They have also recently been the subject of intensive study in view of their peculiar electrophysical and photoelectric properties [1] and their ability to form charge-transfer complexes (CTC) [2].

Several methods for the synthesis of N-heteroaromatic onium betaines of indane-1,3-dione are known. 2-N-Pyridiniaindane-1,3-dione betaine was first obtained in 1951 [3] by a method that seems of little interest for preparative purposes. Another method consisting in the reaction of indane-1,3-dione with pyridine and bromine was proposed in 1952 [4]. The reaction requires a large excess of the N-heteroaromatic base, and it is therefore of little promise for the preparation of indane-1,3-dione onium betaines from other heteroaromatic compounds that are less accessible than pyridine. In 1965 one of us [5] showed that cleavage of an indane-1,3-dione 2-phenyliodonium betaine in the presence of an N-heteroaromatic base is suitable for the preparation of indane-1,3-dione onium betaines. Somewhat later one of us [6] showed that indane-1,3-dione onium betaines can be obtained by reaction of phthalic anhydride with heteronia-substituted acetic acids in the presence of acetic anhydride and triethylamine.

The methods indicated above are not universal, and it therefore became necessary to develop a general method for the preparation of N-heteroaromatic indane-1,3-dione onium betaines. It occurred to us to use

TABLE 1. 2-Dicyanomethyleneindane-1,3-diones (I) and Corresponding Oxides (II)

Compound	X	Y	mp, °C (dec.)	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
Ia	H	H	Lit.[7, 8]		—						—
Ib	Cl	H	250[a]	59,5	1,1	11,4	$C_{12}H_3ClN_2O_2$	59,4	1,2	11,6	70
Ic	H	Cl	248[b]	59,2	1,1	11,5	$C_{12}H_3ClN_2O_2$	59,4	1,2	11,6	70
Id	Br	H	265[b]	50,4	1,0	10,0	$C_{12}H_3BrN_2O_2$	50,2	1,1	9,8	65
IIa	H	H	204[c]	64,5	1,8	12,5	$C_{12}H_4N_2O_3$	64,3	1,7	12,5	92
IIb	Cl	H	208[d]	Cl 13,5	—	10,6	$C_{12}H_3ClN_2O_3$	Cl 13,7	—	10,8	88
IIc	H	Cl	212[e]	Cl 14,0	—	10,9	$C_{12}H_3ClN_2O_3$	Cl 13,7	—	10,8	88
IId	Br	H	207[c]	Br 26,0	—	9,2	$C_{12}H_3BrN_2O_3$	Br 26,4	—	9,2	85

[a]From dioxane–ethanol (1:1). [b]From dioxane. [c]From chlorobenzene. [d]From dioxane–benzene (1:2). [e]From dioxane–chloroform (1:2).

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