ADDITION OF THIIRANES TO Δ^1-PIPERIDEINES AND Δ^1-PYRROLINES

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The reaction of 2,3,4,5-tetrahydropyridines and 1-pyrrolines with thiiranes, which leads to perhydrothiazolo[2,3-a]pyridines and perhydropyrrolo[2,1-b]thiazoles, is described. The regiospecificity and stereoselectivity of the reaction are examined.

As we have recently shown [1], thiiranes add to the C=N bond of acyclic azomethines to give thiazolidines – a class of organic compounds, many representatives of which have a broad spectrum of biological activity and a number of valuable properties [2].

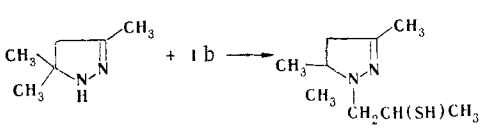
In order to ascertain the limits of applicability of this reaction we investigated the addition of thiiranes to compounds that have an endocyclic azomethine bond. In the case of 1-pyrroline and Δ^1-piperideine derivatives one might have expected the formation of thiazolidines that are condensed with the pyrrolidine or piperidine ring. Such condensed systems are of particular interest in connection with the intensive study of the stereochemistry of heteroanalogs of bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane with a nitrogen atom at the bridgehead (for example, see [3] and the literature cited therein). However, perhydropyrrolo[2,1-b] thiazoles are completely unknown, and the synthesis of the little-studied perhydrothiazolo[3,2-a]pyridines have been realized only recently on the basis of the reaction of tetrahydropyran-2-ol aziridines and hydrogen sulfide [4]. In the course of our systematic study of the reaction of thiiranes with azomethines there was a report [5] in which the addition of thiiranes to the C=N bond of several alkaloids, which leads to the production of polycyclic systems that contain a thiazolidinopyridine fragment, was described.

We have established that thiiranes Ia-c and cyclic imines IIa-e form adducts III and V in V in 30-90% yields (Table 1) when they are heated for 20 h in a mixture of alcohol and benzene. The certain decrease in the yield when dimethylthiirane Ic is used is evidently associated with incomplete conversion of the latter. This reaction can also be used successfully for the synthesis of polycyclic systems; thus cyclohexene sulfide (Id) reacts smoothly with pyrrolines and piperidines to give adducts of the IV and VI type, respectively, while dihydroisoquinoline IIf, the reactivity of which is decreased because of conjugation of the azomethine bone with the aromatic ring [1], is converted to tetrahydrothiazolo[2,1-a]isoquinoline derivative VII in ∿40% yield.

It is known that compounds with an endocyclic C=N bond that are unsubstituted at the azomethine carbon atom readily undergo trimerization [6]. However, the reversibility of the trimerization process when heat is applied makes it possible in a number of cases to use the trimers as the synthetic equivalents of the monomers [6, 7]. As we have shown, the reaction of thiiranes with trimeric azomethines IIa,d leads to the corresponding adducts in high yields.

We obtained the perhydrothiazolopyridine IIIa described in [4] in 60% yield; as compared with the known method for the synthesis, our method is appreciably simpler and safer.

We were unable to obtain adducts of methylthiirane (which usually reacts most smoothly with azomethines) with 2-methoxy-1-pyrroline and 5-methyl-1-ethylpyrazoline, whereas with 5,5,5-trimethyl-2-pyrazoline we obtained only a product of mercaptoalkylation in the 1 position (VIII).



VIII

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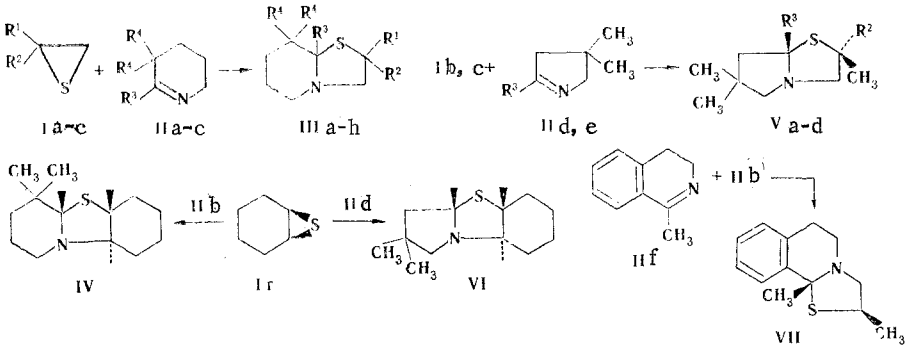
TABLE 1. Perhydrothiazolopyridines and Perhydropyrrolothiazoles

Compound	bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	Yield, %
IIIa	100—101 (14)[a]	—	1,5410	63
IIIb	98—99 (13)	1,0292	1,5211	67
IIIc	88—89 (8)	0,9857	1,5045	32
IIId	104—105 (12)	1,0261	1,5207	82
IIIe	106—107 (12)	0,9891	1,5063	90
IIIf	106—107 (12)	0,9620	1,4964	73
IIIg	116—117 (8)	1,0086	1,5170	79
IIIh	114—115 (8)	0,9782	1,5050	37
IV	133—136 (3)[b]	1,0243	1,5258	69
Va	87—88 (8)	0,9883	1,5020	75
Vb	95—96 (12)	0,9638	1,4930	58
Vc	84—85 (8)	0,9629	1,4935	72
Vd	86—87 (8)	0,9480	1,4879	35
VI	111—113 (3)	1,0324	1,5264	54
VII	133—136 (1, 5)	1,1081	1,5887	42

[a]Data from [4]: bp 68°C (3 mm), n_D^{20} 1.5402.
[b]This compound has mp 37-38°C.

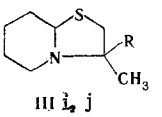


I a $R^1=R^2=H$; b $R^1=Me$, $R^2=H$; c $R^1=R^2=Me$; II a $R^3=R^4=H$; b $R^3=H$, $R^4=Me$; c $R^3=R^4=Me$; d $R^3=H$; e $R^3=Me$; III a $R^1=R^2=R^3=R^4=H$; b $R^1=Me$, $R^2=R^3=R^4=H$; c $R^1=R^2=Me$, $R^3=R^4=H$; d $R^1=R^2=R^3=H$, $R^4=Me$; e $R^1=R^4=Me$, $R^2=R^3=H$; f $R^1=R^2=R^4=Me$, $R^3=H$; g $R^1=R^3=R^4=Me$, $R^2=H$; h $R^1=R^2=R^3=R^4=Me$; V a $R^2=R^3=H$; b $R^2=Me$, $R^3=H$; c $R^2=H$, $R^3=Me$; d $R^2=R^3=Me$

A possible reason for the lack of success in these cases is stabilization of the azomethine bond as a consequence of p,π conjugation (see also [1]). However, we were also unable to subject 1-acetyl-3,5,5-trimethyl-2-pyrazoline, in which the unshared electron pair of the $N_{(1)}$ atom is partially blocked, to reaction with methylthiirane.

We have shown [1] that acyclic imines react with methyl- and 2,2-dimethylthiirane regioselectively to give 5-methyl-substituted thiazolidines. One therefore should have expected that the methyl groups in the adducts of these thiiranes with pyrrolines and piperideines are located in the 2 position. This assumption is confirmed by the fact that IIIc,e proved to be identical to the known [4] isomeric 3-methyl- and 3,3-dimethylperhydrothiazolo[3,2-a]-pyridines (IIIi, j, respectively).

The PMR spectra of the adducts of pyrrolines and piperideines with thiirane or dimethylthiirane corresponds to individual compounds (Tables 2 and 3). At the same time, two sets of



III i, j III i R=H; j R=CH_3

signals that correspond to two epimers are present in the spectra of a number of adducts obtained on the basis of methylthiirane; the amounts of epimers are comparable in the case of IIIb, e, g, whereas their ratio is no less than 10:1 for the remaining adducts.

In solutions perhydrothiazolo[3,2-a]pyridines exist in the form of a mixture of trans- and cis-fused forms that undergo interconversion as a result of inversion of the nitrogen

TABLE 2. PMR Spectra of Perhydrothiazolo[3,2-a]pyridines[a]

Compound	Isomer[b]	δ, ppm (J, Hz)						
		2-H	3-H	3'-H	8a-H	5-H_a	5-H_e	CH_3
IIIa	—	2,6—3,3			4,18 (8,2)[c]	2,6—2,8		—
	cis (70)	3,64	2,22	3,18 ($^3J_{23}$=9,8; $^3J_{23'}$=6,1; $^2J_{33'}$=−10,8)	4,21 ($^3J_{8a}$≈ ≈3,6 and 5,1)	—[d]		1,28 (6,5)
IIIb	trans (30)	3,30	2,53	2,77 ($^3J_{23}$=6,2; $^3J_{23'}$=8,7; $^2J_{33}$=−9,5)	3,36 ($^3J_{8a}$≈ ≈2,9 and 9,4)	—[d]		1,34 (6,8)
IIIc	—		2,27	2,80 (−9,2)	3,47 ($^3J_{8a}$≈ ≈2,9 and 9,5)	2,05	3,04	1,38 and 1,43
IIId	—	2,3—2,9			3,68	2,12	3,18	0,99
	cis (60)	3,48	2,15	3,21 ($^3J_{23}$=9,9; $^3J_{23'}$=5,8; $^2J_{33'}$=−9,9)	3,72	—[d]		0,93 and 1,00 s; 1,26 (6,2)
IIIe	trans (40)	3,30	2,50	2,89 ($^3J_{23}$=5,8; $^3J_{23'}$≤0,5; $^2J_{33'}$=−9,1)	3,22	—		0,84 and 1,07 s; 1,32 (7,0)
IIIf	—	—	2,30	2,78 (−8,9)	3,38	2,03	3,02	0,79; 1,06; 1,36; 1,44
	cis (75)	3,61	2,81	3,05 ($^3J_{23}$=9,5; $^3J_{23'}$=6,6; $^2J_{33'}$=−11,7)	—	1,62	2,53	1,02, 1,08 and 1,46 s; 1,28 d (6,5)
IIIg	trans[e] (25)	—	—	—	—	—	—	0,94, 1,20 and 1,33 s; 1,35 d (7,0)
IIIh	—	—	2,69	2,89 (−9,4)	—	2,5		0,86; 1,28; 1,36; 1,39; 1,45
IV	—	2,76[f]	3,03[g]	—	3,37	—[d]		0,83 and 1,01
VII[h]	—	3,78	3,17	3,27 ($^3J_{23}$=10,3; $^3J_{23'}$=5,1; $^2J_{23'}$=−12,8)	—	—	—	1,84 s; 1,31 d (6,4)

[a]Solutions in tetrachloroethylene at 30°C. The protons in the 6, 7, and 8 positions give a multiplet signal at 1-2 ppm. [b]The relative orientation of the angular substituent and the methyl group in the 2 position is indicated. The percentage of the isomer in the mixture is given in parentheses. [c]The $\Sigma\,^3J_{8\,8a}$ value is presented. [d]The signals of these protons are overlapped with the signals of the protons of the other methylene groups. [e]Only the signals of the methyl groups of this isomer were identified. [f]The width of the multiplet signal was 24 Hz. [g]The width of the multiplet signal was 20 Hz. [h]The signals of the 5- and 6-H protons are observed in the form of a multiplet at 2.4-3.1 ppm, while the signals of the aromatic protons are observed at 6.7-7.2 ppm.

atom; for the cis form one must also take into account yet another possibility of conformational transitions due to ring conversion [8].

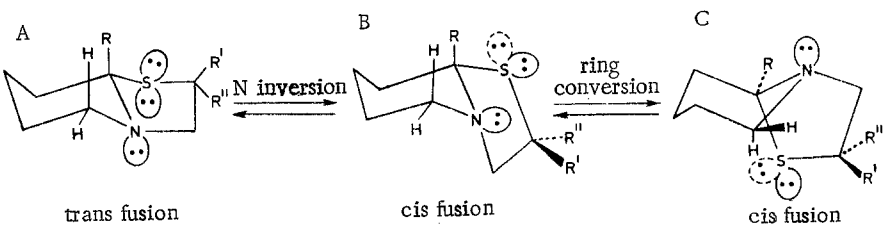


TABLE 3. PMR Spectra of Perhydropyrrolo[2,1-b]thiazoles[a]

Compound	δ, ppm (J, Hz)								
	2-H	3-H	3′-H	5-H	5′-H	7-H	7′-H	7a-H	Me
Va[b, c]	3,75 ($^3J_{23}$=5,7; $^3J_{23'}$=9,7; $^2J_{33'}$=−12,6)	3,31	2,47	2,50 (−8,0)	2,56	1,90 ($^3J_{77a}$=2,5; $^3J_{7'7a}$=6,7; $^2J_{77'}$=−13,5)	2,05	4,95	1,12 s; 1,26 d (6,3)
Vb	—	2,85 (−11,3)	2,94	2,66 (−8,0)	2,87	1,83 ($^3J_{77a}$=5,0; $^3J_{7'7a}$=6,6; $^2J_{77'}$=−13,0)	1,96	5,02	1,12, 1,43, 1,50
Vc[b, d]	3,86 ($^3J_{23}$=9,8; $^3J_{23'}$=6,0; $^2J_{33'}$=−12,9)	2,65	3,29	2,56 (−8,2)	2,65	1,77 (−13,4)	2,33	—	1,07, 1,12 and 1,53 s; 1,26 d (6,3)
Vd	—	3,07		2,66 (−8,2)	3,20	1,70 (−13,4)	2,31	—	1,08, 1,10, 1,42, 1,53, 1,56
VI	2,50	3,13[e]	—	2,35 (−8,1)	2,43	1,90 ($^3J_{77a}$=3,2; $^3J_{7'7a}$=7,1; $^2J_{77'}$=−13,4)	2,08	4,89	1,10, 1,13

[a]Solutions in tetrachloroethylene at 30°C. [b]The data for the principal epimer with the 2-Me and 7a-R groups in the cis orientation are presented; the fraction of the second epimer did not exceed 10%. [c]Only the signals of the 7a-H proton at 4.83 ppm (Σ^3J_{77a} = 8.9 Hz) and the CH_3 groups at 1.14 (s) and 1.42 ppm (d, J = 6.4 Hz) were identified for the trans isomer. [d]Only the signals of the methyl groups at 1.09, 1.12, 1.47 (singlets), and 1.43 ppm (d, J = 6.5 Hz) were identified for the trans isomer. [e]The width of the multiplet was 23.5 Hz.

The cis-fused form (B) is less favorable than trans-fused A, in which syn-axial interactions are absent, and also less favorable than the C conformer, the stability of which is ensured by an anomeric effect — the approximate orthogonality of the unshared electron pairs of the nitrogen and sulfur atoms [8, 9]. Therefore, despite the fact that the B form is an intermediate in the A $\rightleftarrows$ C interconversion, its contribution to the equilibrium can be disregarded. The A $\rightleftarrows$ C stepwise equilibrium leads to averaging of the vicinal spin–spin coupling constants in the PMR spectra of compounds of the III type. For the 8a-H proton, the signal of which in the spectra of IIIa-c corresponds to the X part of an ABX system, $\Sigma^3J_{obs} = N_A\Sigma^3J_A + (1 - N_A)\Sigma^3J_B$. Assuming that Σ^3J_B = 5.2 Hz [8], Σ^3J_A = 12.4 Hz (the maximum of the values observed in this research; see also [8]), it is not difficult to estimate the A $\rightleftarrows$ C equilibrium constant $K = (1 - N_A)/N_A$.

For unsubstituted IIIa, K = 1.3 (in C_2Cl_4 at 30°C), which virtually coincides with the value obtained in [8] for a solution in CS_2 at 36°C.

In the case of substituted compounds of the III type the position of the A $\rightleftarrows$ C equilibrium depends on the numbers and positions of the substituents, as well as on their spatial orientation. Thus, in the case of perhydrothiazolopyridine IIIi with a cis-oriented angular proton and a methyl group the C form somewhat predominates, whereas for its trans epimer the A form predominates somewhat, and for dimethyl-substituted IIIj the equilibrium is shifted markedly to favor the trans-fused A form [8].

The isomeric (with respect to the latter compound) 2,2-dimethylperhydrothiazolopyridine IIIc, according to our data (Table 2, $\Sigma^3J_{obs} = \Sigma^3J_A$ = 12.4 Hz), exists virtually entirely in the trans-fused A form. This shift in the equilibrium must be associated with the pronounced destabilizing interaction of one of the methyl groups with the 5-H_a atom in the C conformation. The conclusion that the equilibrium is shifted precisely in this direction is confirmed, first of all, by the appreciable difference in the width of the signals of the 5-H_a and 5-H_e protons (25 and 18 Hz, respectively), which is approximately equal to the typical $^3J_{aa} - {}^3J_{ee}$ difference in the six-membered rings and, second, by the large difference (∿1 ppm) in the chemical shifts of the same protons. This situation is extremely characteristic for compounds that have a methylene group in the six-membered ring adjacent to the nitrogen atom at the bridgehead vis-à-vis marked preponderance of the conformer with the axial orientation of the unshared pair of the nitrogen atom [10, 11].

The signal of the 8a-H proton with ε 3.36 ppm and Σ^3J_{obs} = 8.7 Hz corresponds to the principal epimer of IIIb in the PMR spectrum (Table 2), and hence it follows that K = 1.0, i.e., the populations of both the A and C forms are the same. For the epimer that is present in smaller amounts, K < 0.1 (Σ^3J_{obs} = 12.3 Hz). It might be expected that the C conformation is markedly destabilized only in the case of the epimer of IIIb, which has a 8a-H proton and a 2-Me group in the trans orientation (similar to the IIIc molecule). Thus the cis-2-Me, 8a-H isomer predominates in the mixture of perhydrothiazolopyridines IIIb.

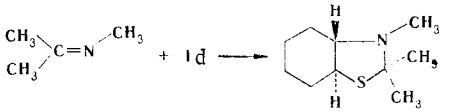
The Σ^3J_{obs} value cannot be used as a criterion for the establishment of the spatial structures of IIId-f, in the PMR spectra of which the signal of the 8a-H proton is a singlet.

In the spectrum of perhydrothiazolopyridine IIId the difference in the chemical shifts of the 5-H_a and 5-H_e protons is close to 1 ppm, whereas the widths of the signals are 22 and 17 Hz, respectively. This indicates preponderance of one of the stereoisomeric forms. An analysis of Dreiding models makes it possible to assume that the C structure with minimal destabilizing interaction of the sulfur atom with the gem-dimethyl grouping is the most probable structure.

Compound IIIe was isolated in the form of a mixture of epimers in an approximate ratio of 3:2. Considering the certain analogies in the spectra of spimers IIIe and IIIb, it might be expected that principal isomer IIIe has the 2-Me group and the 8a-H proton in a cis orientation. This was confirmed by means of the Overhauser nuclear effect: the intensity of the 8a-H signal increased by 8-9% when the 2-Me group of this epimer was irradiated. It is not possible to give a quantitative evaluation of the position of the A $\rightleftarrows$ C equilibrium for either both epimers of IIIe or for perhydrothiazolopyridine IIIf. With allowance for the shifts of the 8a-H proton one can only assume an appreciable (trans-isomer IIIe) or complete (IIIf) shift of this equilibrium to favor the trans-fused A form. Let us mote that trans-fusion of the rings is evidently realized exclusively for the protonated IIIe molecules: in the PMR spectrum in trifluoroacetic acid the 8a-H protons of both epimers have close chemical shifts and identical $^3J_{4_{8_a}}$ constants of 10.2 Hz, which indicate a trans-diaxial orientation of the interactiong protons.

For IIIg, h which contain simultaneously 8,8-gem-dimethyl and 8a-methyl groups, the conformational composition is probably determined by pronounced steric compression of the latter in the case of its equatorial orientation. This leads to predominance of the A structure. However, it is difficult to reliably establish the configuration of the epimers of IIIg and the character of the ring fusion in the IIIg, h moleculesfrom the PMR spectral data.

To ascertain the stereochemistry of opening of the thiirane ring we carried out the reaction of acetone methylimine with 1,2-epithiocyclohexane:



IX

Judging from the PMR spectrum, only one stereoisomer of 2,3,3-trimethylperhydrobenzothiazole (IX) is formed in this case. The width of the signals of the 3a- and 7a-H protons (23-24 Hz) indicates unambiguously their trans-diaxial orientation. The reaction consequently proceeds with inversion of the configuration of the thiirane carbon atom undergoing attack.

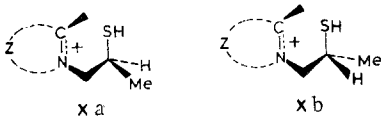
Considering this result, in the reaction of episulfide Id with tetrahydropyridine IIc and with dihydroisoquinoline IIf one should have expected the formation of no more than two stereoisomeric adducts. It was found that virtually only one isomer is formed in both cases. In the case of 2,3-tetramethyleneperhydrothiazolopyridine IV the strong-field position of the signal of the 8a-H proton more likely corresponds to a cis orientation than to a trans orientation of the 2- and 8a-H protons. Preponderance of the structure with trans,trans ring fusion therefore seems most likely. The PMR spectra do not make it possible to determine the configuration of VII.

On the basis of the PMR spectra one also cannot reliably establish the three-dimensional structures of perhydropyrrolothiazoles Va-d. An analysis of Dreiding models makes it possible to assume that primarily (if not completely) the trans-fused form is realized in the case of Vb. A comparison of the PMR spectra in the region of 7a-H resonance, if this assumption is valid, leads to the conclusion that the principal epimer of perhydropyrrolothiazole Va and

three-ring compound VI have the same three-dimensional structure. In the case of epimer Va, which is present in smaller amounts, a significant contribution of the cis-fused form is likely.

We have established that the reaction of azomethines with thiiranes can be catalyzed by alcohols and proceeds as nucleophilic opening of the episulfide ring [1].

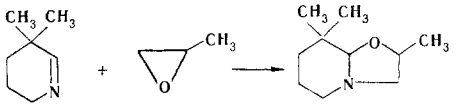
We observed that the reaction of tetrahydropyridines IIb, c with methylthiirane leads to reaction products IIIe, g, which have the same stereoisomeric composition, regardless of whether one uses dry benzene or a mixture of dry benzene with ethanol as the solvent. The ratio of the stereoisomers remains virtually unchanged when the adducts are heated for several hours with 15% sulfuric acid or in the presence of 10% anhydrous trifluoroacetic acid with subsequent isolation of the free bases by alkalization. It is known that thiazolines undergo reversible hydrolysis in water in the case of acidic catalysis [12], whereas in anhydrous media in the presence of trifluoroacetic acid they could, like oxazolidines and imidazolidines [13], undergo equilibrium isomerization to immonium salts. Our observed retention of the stereoisomeric composition of the perhydrothiazolopyridines indicates that it is formed, in all lieklihood, in the step involving cyclization of the intermediate immonium structures. Of the two transition states that develop during approach of the nucleophile (the thiol group or the thiolate anion) to the diastereotopic sides of the immonium fragment, Xa, with an exo-oriented methyl group, is more easily realized for steric reasons. It should therefore be preferable to obtain adducts that have a 2-Me group and an angular substituent in a cis orientation.



x a x b

The ratio of the epimers in this case is determined by the conformational lability of connecting link Z and the position of the substituents in it relative to the reaction center. Proceeding from this prerequisite, a cis configuration (as in the case of perhydrothiazolopyridines IIIb, d) was assigned to the principal epimers of IIIg, Va, c, and VII. A similar configuration of three-ring systems IV and VI [cis-2-H, 8a(7a)-H] also seems more likely, since in the alternative variant the transition state for cyclization proves to be more strained (from an analysis of Dreiding models).

In order to compare the stereochemical peculiarities of the reactions involving addition to the azomethine bond of thiiranes and oxiranes we subjected tetrahydropyridine IIb to reaction with methyloxirane. The reaction of azomethines with oxiranes to give oxazolidines is known [14]; however, this reaction usually proceeds under relatively severe conditions. We have established that IIb and methyloxirane react smoothly upon heating in alcohol to give perhydrooxazolopyridine XI in high yield:



II b XI

As in the case of methylthiirane, an adduct is produced in the form of a mixture of two stereoisomers, except that one of them predominates slightly. The PMR spectra of both isomers bear certain analogies to the spectra of the isomeric perhydrothiazolopyridines IIIe. In both cases the signal of the 8a-H proton of the isomer that is present in the mixture in somewhat greater amounts is observed at weaker field, and the difference in the chemical shifts of the geminal 3-H protons exceeds 1 ppm. The cis isomer evidently develops primarily from methyloxirane. The very small value of one of the $^3J_{23}$ constants for the corresponding trans isomers ($\leq$0.5 Hz for IIIe and 1.8 Hz for XI) is also remarkable. If one takes into account the fact that for all of the remaining condensed thiazolidines the $^3J_{23}$ values do not differ so significantly from the corresponding values for monocyclic 5-alkylthiazolidines ($^3J_{45}^{cis}$ = 5.8-6.5, $^3J_{45}^{trans}$ = 7.5-8.8 Hz [15]), one should assume a marked change in the three-dimensional structure of the thiazolidine fragment in the trans isomer of IIIe. In all likelihood, this change is due to strong steric interaction between the methyl groups of the piperidine and thiazolidine rings.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra of 20% solutions of the compounds in tetrachloroethylene (except for the specially stipulated cases) were obtained with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane as the internal standard. The individuality of the compounds obtained were confirmed by gas-liquid chromatography (GLC) with a Tsvet-101 chromatograph equipped with a 2-m × 3-mm glass silanized column filled with 5% SE-30 on Inerton-AW (0.125-0.16 mm).

Thiirane obtained by the method in [16], methylthiirane obtained by the method in [17], 2,2-dimethylthiirane obtained by the method in [18], and 1,2-epithiocyclohexane obtained by the method in [17] were used in this research.

2,3,4,5-Tetrahydro-5,5-dimethylpyridine (IIb). This compound was synthesized from 4,4-dimethyl-4-formylvaleronitrile [19] by the method in [20] and had bp 146-147°C, and n_D^{20} 1.4533 (bp 144.5-145.0°C [19]). IR spectrum (3% solution in CCl_4): 1660 (C=H) and 3030 cm^{-1} (=C–H). PMR spectrum (CCl_4): 0.99 (s, 5-Me), 1.4-1.6 (m, 3- and 4-H), 3.44 (m, 2-H), and 7.39 ppm (t, $^4J_{26}$ = 2 Hz, 6-H).

2,3,4,5-Tetrahydro-5,5,6-trimethylpyridine (IIc). A mixture of 106 g (0.76 mole) of 4,4-dimethyl-5-oxohexanenitrile [21], 56 g (0.90 mole) of ethylene glycol, 250 ml of benzene, and 0.5 g of p-toluenesulfonic acid was refluxed with a Dean–Stark trap until 15 ml of water had separated, after which the mixture was washed with sodium bicarbonate and water, dried, and distilled to give 119 g (86%) of 5,5-ethylenedioxy-4,4-dimethylhexanenitrile with bp 102-104°C (2 mm) and n_D^{20} 1.4559. This nitrile was dissolved in 180 ml of methanol and hydrogenated by the addition of 12 g of Raney nickel and 25 g of liquid ammonia; the hydrogenation was carried out in a steel autoclave at 80-110°C and 14-18 MPa. The catalyst was removed by filtration, the methanol was removed by distillation, and the residue was refluxed for 5 h with 200 ml of 7.5 N hydrochloric acid. The cooled solution was saturated carefully with solid potassium hydroxide until layers separated completely, and the organic layer was combined with the ether extract from the aqueous layer, dried, and distilled to give 55 g (58%) of piperideine IIc with bp 166-168°C (760 mm), bp 76-78°C (40 mm), and n_D^{20} 1.4620 [bp 70°C (40 mm) and n_D^{20} 1.4616 [22]]. IR spectrum (3% solution in CCl_4): 1650 cm^{-1} (C=N). PMR spectrum (CCl_4): 1.05 (s, 5-Me), 1.35-1.70 (m, 3- and 4-H), 1.82 (t, $J_{6\text{-Me},2\text{-H}}$ = 1.8 Ha, 6-ME), and 3.35-3.50 ppm (m, 2-H).

4,4-Dimethyl-1-pyrroline (IId). A 69-g (1.0 mole) sample of isobutyronitrile, 197 g (1.0 mole) of bromacetal, and 300 ml of absolute ether was placed in a flask equipped with a stirrer, dropping funnel, and a gas-inlet tube, and a solution of lithium diethylamide, obtained from 7.7 g (1.1 moles) of lithium and 80 g (1.1 moles) of diethylamine, and 480 ml of a mixture of benzene with hexamethylphosphoric triamide (1:1) were added with stirring at –60 to –65°C in a stream of nitrogen in the course of 2 h. Stirring at –60°C was continued for another 30 min, after which the mixture was allowed to warm up to 0°C. It was then poured into 2 liters of water containing ice and acidified with 80 ml of concentrated hydrochloric acid (to pH 8), after which the benzene layer was separated, and the aqueous layer was extracted several times with ether. The extracts were combined with the benzene layer and dried with magnesium sulfate. The solvents were removed by distillation, and the residue was distilled in vacuo to give 120 g (62%) of 2,2-dimethyl-4,4-diethoxybutyronitrile with bp 97-98°C (9-10 mm) and n_D^{20} 1.4223 [bp 116-118°C (30 mm) [23]]. This nitrile was dissolved in 130 ml of methanol and hydrogenated in an autoclave with the addition of 10 g of Raney nickel and 27 g of liquid ammonia; the hydrogenation was carried out at 105-110°C and 10-15 MPa. The reaction mixture was then worked up as in the preparation of IIc. Distillation with a column gave 20 g (34%) of pyrroline IId as a colorless liquid with an unpleasant odor. Upon storage it underwent rapid trimerization to 4arH,8acH,12acH-perhydro-2,2,6,6,10,10-hexamethyltris(pyrrolo[2,1-a:2,1-c:2,1-e]-1,3,5-triazinyl) with mp 42-44°C; this product was converted to the monomer when it was heated above 120°C. PMR spectrum: 1.04 and 1.13 (s, 2-, 6-, and 10-Me), 1.51 (d, J = 6.3 Hz, 1-, 5-, and 9-H), 2.00 and 2.76 (dd, J = 8 Hz, 3-, 7-, and 11-H), and 2.98 ppm (t, J = 6.3 Hz, 4a-, 8a-, and 12a-H). Found: C 74.4; H 11.6%. $C_{18}H_{33}N_3$. Calculated: 74.2; H 11.4%.

2,4,4-Trimethyl-1-pyrroline (IIe). This compound, with bp 128-129°C and n_D^{20} 1.4311 (bp 126-129°C [24]), was obtained from mesityl oxide and nitromethane by the method in [24].

1-Methyl-3,4-dihydroisoquinoline (IIf). This compound was obtained by the Bischler–Napieralski method and had bp 234-237°C [25].

General Method for the Preparation of Condensed Thiazolidines III-VII. A solution of 0.04-0.1 mole of the thiirane and 0.04-0.12 mole of the azomethine in 60-100 ml of a mixture of alcohol and benzene (2:3) was heated in a steel autoclave at 100°C for 20 h, after which the solvent was removed by distillation, and the residue was fractionated twice in vacuo. In the case of VI and VII repeated distillation was replaced by purification with a chromatographic column filled with a preadsorption layer of an inert support; the sorbent was activity II aluminum oxide, and the eluent was ether–pentane (0:1 → 0.3:1). The principal characteristics of the compounds obtained are presented in Table 1, while the analytical data for their picrates are presented in Table 4.

2,2,3,3-Trimethyl-trans-perhydrobenzothiazole (IX). This compound, with bp 112-113°C (11 mm), d_4^{20} = 1.0037, and n_D^{20} 1.5144, was obtained in 24% yield from acetone methylimine [26] and cyclohexene sulfide by the method presented above. PMR spectrum: 1.32 and 1.46 (s, 2-Me), 2.15 (s, 3-Me), 2.35 (m, broad signal, 23.4 Hz, 3a-H), 2.90 (m, broad signal, 23.6 Hz, 2a-H), and 1.7-2.0 ppm (m, 4-, 5-, 6-, and 7-H). The picrate has mp 176-178°C (from alcohol). Found: C 46.2; H 5.4; N 13.2; S 7.7%. $C_{10}H_{19}NS \cdot C_6H_3N_3O_7$. Calculated: C 46.4; H 5.4; N 13.5; S 7.7%.

1-(3,5,5-Trimethyl-2-pyrazolin-1-yl)-2-propanethiol (VIII). The reaction of 3,5,5-trimethyl-2-pyrazoline [27] with methylthiirane was carried out by the method described above for the preparation of III-VII. After the first distillation, the reaction product was purified by means of column chromatography and distilled once again to give a product with bp 72-74°C (3 mm) and n_D^{20} 1.4969 in 42% yield. IR spectrum (thin layer): 1617 (C=N) and 2650 cm^{-1} (SH). PMR spectrum (CCl_4): 1.04 and 1.12 (s, diastereotopic 5'-Me); 1.25 (dd, $^3J_{32}$ = 7.0 Hz, $^4J_{3\text{-H,SH}}$ = 0.8 Hz, 3-H); 1.84 (t, $^4J_{3'\text{-Me},4'\text{-H}}$ = 2.1 Hz, 3'-Me); 1.91 (m, $^3J_{2\text{-H,SH}}$ = 4.6 Hz, $^4J_{3\text{-H,SH}}$ = 0.8 Hz, SH); 2.31 (m, 4'-H), 2.58, 2167, and 3.27 ppm (ABX system, J_{AB} = −11.9, J_{AX} = 5.7, J_{BX} = 7.9 Hz, 1- and 2-H). Found: C 58.0; H 9.7%. $C_9H_{18}N_2S$. Calculated: C 58.0; H 9.7%.

3,7,7-Trimethylperhydrooxazolo[3,2-a]pyridine (XI). The reaction of piperideine IIb with methoxirane was carried out in the same way as the reaction with methylthiirane using ethanol as the solvent. Workup gave XI with bp 77-78°C (13 mm), d_4^{20} 0.9339, and n_D^{20} 1.4598 in 78% yield. The ratio of the cis isomer to the trans isomer was ∿55:45. PMR spectrum: for the cis isomer: 4.06 (m, 2-H), 3.13 (dd, 3-H), 1.97 (dd, 3'-H, $^3J_{23}$ = 5.7, $^2J_{23'}$ = 8.7, and $^3J_{33'}$ = −8.8 Hz), and 3.22 (s, 8a-h); for the trans isomer: 3.98 (m, 2-H), 2.69 (dd, 3-H), 2.39 (dd, 3'-H, $^3J_{23}$ = 1.8, $^3J_{23'}$ = 8.2, and $^2J_{33'}$ = −8.0 Hz), and 3.07 ppm (s, 8a-H); in addition, we observed signals at 1.15 (d, J ≈ 6 Hz, 2-Me of both stereoisomers), four singlets at 0.90-0.95 (i-Me), and multiplets at 2.80-3.95 (5-H_a), 1.90-2.20 (5-H_e), and 1.40-1.80 ppm (6- and 7-H). The picrate has mp 115-117°C (from alcohol). Found: C 48.2; H 5.2; N 13.7%. $C_{10}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated: C 48.2: H.5.6; N 14.1%.

TABLE 4. Picrates of the Perhydrothiazolopyridines and Perhydropyrrolothiazoles

Base	Picrate									
	mp, °C (from alcohol)	Found, %				Empirical formula	Calc., %			
		C	H	N	S		C	H	N	S
IIIb	112—115	43,5	4,7	14,6	8,3	$C_8H_{15}NS \cdot C_6H_3N_3O_7$	43,5	4,7	14,5	8,3
IIIc	128—130	45,2	4,9	14,1	8,0	$C_9H_{17}NS \cdot C_6H_3N_3O_7$	45,0	5,0	14,0	8,0
IIId	194—195	44,9	5,2	13,9	7,9	$C_9H_{17}NS \cdot C_6H_3N_3O_7$	45,0	5,0	14,0	8,0
IIIe	143—146	46,6	5,3	13,4	7,5	$C_{10}H_{19}NS \cdot C_6H_3N_3O_7$	46,4	5,4	13,5	7,7
IIIf	166—168	47,6	5,6	13,2	7,1	$C_{11}H_{21}NS \cdot C_6H_3N_3O_7$	47,7	5,6	13,1	7,5
IIIg	168—169	47,5	5,7	12,9	7,7	$C_{11}H_{21}NS \cdot C_6H_3N_3O_7$	47,7	5,6	13,1	7,5
IIIh	159—160	48,8	6,1	12,4	7,4	$C_{12}H_{23}NS \cdot C_6H_3N_3O_7$	48,9	5,9	12,7	7,2
IV	187—188	50,2	5,8	12,0	7,2	$C_{13}H_{23}NS \cdot C_6H_3N_3O_7$	50,2	5,8	12,3	7,0
Va	121—124	44,9	5,2	14,1	7,9	$C_9H_{17}NS \cdot C_6H_3N_3O_7$	45,0	5,0	14,0	8,0
Vb	115—117	46,4	5,3	13,4	7,8	$C_{10}H_{19}NS \cdot C_6H_3N_3O_7$	46,4	5,4	13,5	7,7
Vc	110—113	46,8	5,5	13,6	7,5	$C_{10}H_{19}NS \cdot C_6H_3N_3O_7$	46,4	5,4	13,5	7,7
Vd	122—124	47,4	5,6	13,1	7,0	$C_{11}H_{21}NS \cdot C_6H_3N_3O_7$	47,7	5,6	13,1	7,5
VI	166—168	49,0	5,9	12,5	7,4	$C_{12}H_{21}NS \cdot C_6H_3N_3O_7$	49,1	5,5	12,7	7,3
VII[a]		70,9	8,1	—	—	$C_{13}H_{17}NS$	71,2	7,8	—	—

[a]The analytical characteristics of the base are presented in this case.

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UREIDO AND THIOUREIDO DERIVATIVES OF β-LACTAM ANTIBIOTICS

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6-Ureido- and 6-thioureidopenicillanic acids and 7-ureido- and 7-thioureidodeacetoxycephalosporanic acids were obtained by the reaction of 6-aminopenicillanic acid and 7-aminodeacetoxycephalosporanic acids with tetraisocyanatosilane or tetraisothiocyanatosilane. N-Carbamoyl derivatives of ureido- and thioureidopenicillanic acids were isolated after repeated treatment of 6-ureido- and 6-thioureidopenicillanic acids with the indicated isocyanatosilanes.

Ureido and thioureido derivatives of β-lactam antibiotics Ia-c are usually obtained by the reaction of amino acids with alkali metal isocyanates or thiocyanic acid [1-5].

7-Ureidodeacetoxycephalosporanic acid (Id), the ureido group in which is directly adjacent to the β-lactam ring, has also been synthesized by means of potassium cyanate [6]. However, the corresponding penicillin analog Ie could not be obtained by this method, since modification of the amino group in aqueous solution at elevated temperatures is accompanied by destruction of the β-lactam ring of the heterocyclic amino acids.

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