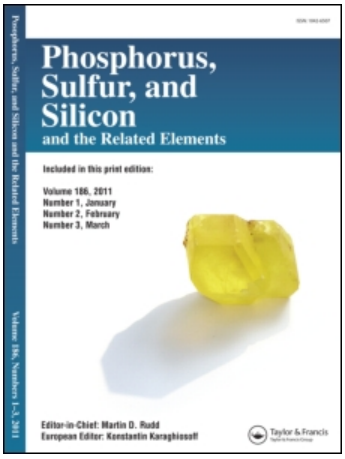

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Advances in the Chemistry of Hydrogenated 3-Cyanopyridine-2(1H)-Thiones and -Selenones

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ADVANCES IN THE CHEMISTRY OF HYDROGENATED 3-CYANO-PYRIDINE-2(1H)-THIONES AND -SELENONES

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Abstract This lecture is concerned with the synthesis, physico-chemical properties and reactivity of an important class of heterocyclic compounds - hydrogenated 3-cyanopyridine-2(1H)-thiones, and -selenones and their derivatives.

INTRODUCTION

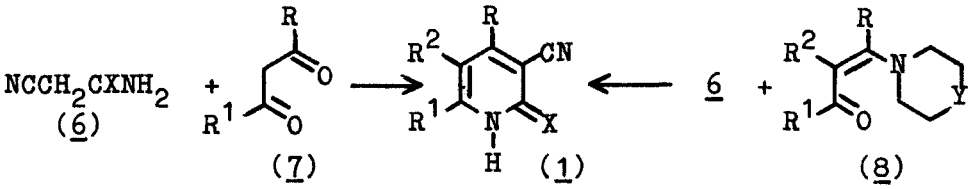
The author's review on chemistry of 3-cyanopyridine-2(1H)-ones, -thiones, and -selenones is to be shortly published in Sulfur Reports [1]. In this lecture, therefore, will be discussed synthesis, physico-chemical properties, and reactivity of hydrogenated 3-cyanopyridine-2(1H)-thiones and -selenones which are of considerable interest both for theoretical organic chemistry and as synthons to prepare novel biologically active compounds.

SYNTHESIS

The majority of methods of synthesis of 3-cyanopyridine-2(1H)-thiones and -selenones and their derivatives (1-5) is based on interaction of cyanothio(seleno)acetamides (6)

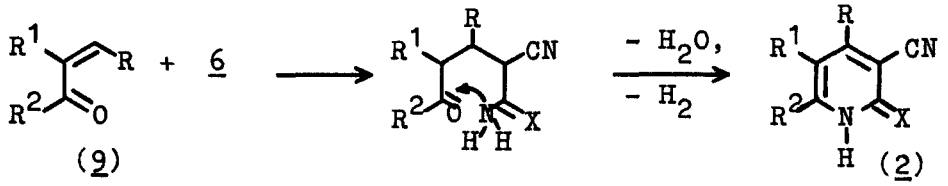
with

i) 1,3-dicarbonyl compounds (7) or enamines (8) derived therefrom:

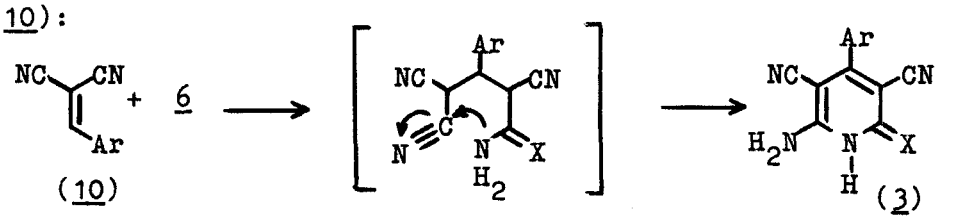


X = S, Se; Y = O, CH_2; R, R^1, R^2 = Alk, Ar

ii) α,β-unsaturated carbonyl compounds (9):

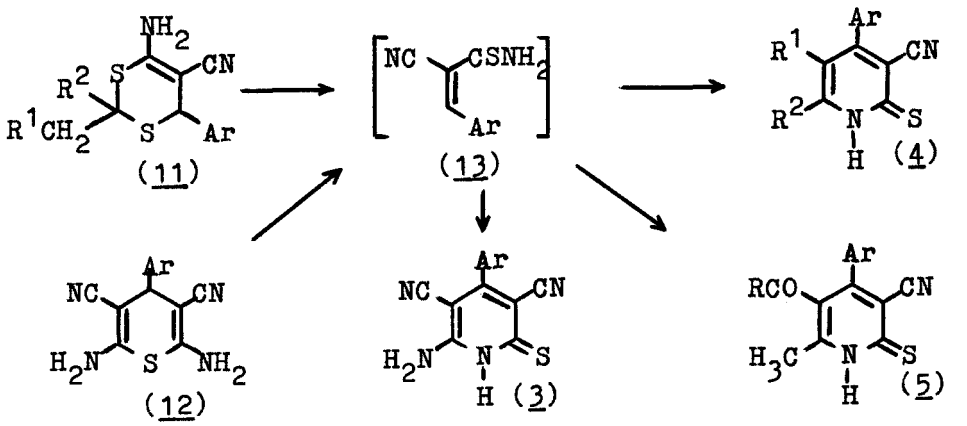


iii) nitriles of α,β-unsaturated carboxylic acids (10):

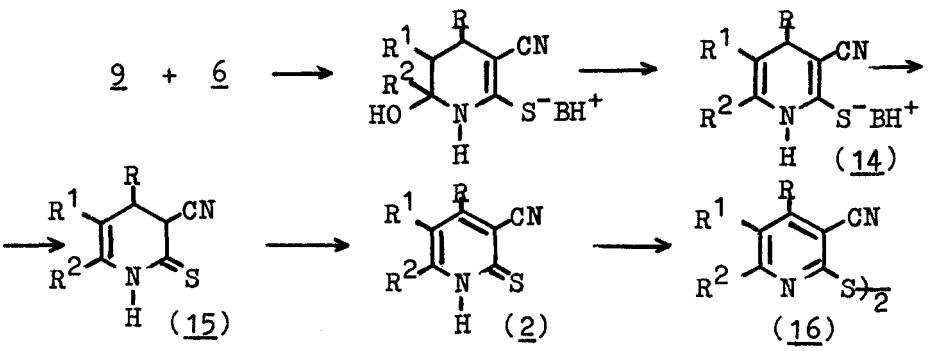


Alternatively, they are produced upon recyclization of 1,3-dithiacyclohexenes (11), 4H-thiopyrans (12), and some other heterocycles [1].

It was in 1980 that the formation of 3-cyano-3,4-dihydropyridine-2(1H)-thiones as intermediates in condensation of arylideneacetone or arylideneacetophenone with cyanothioacetamide was observed for the first time [2].

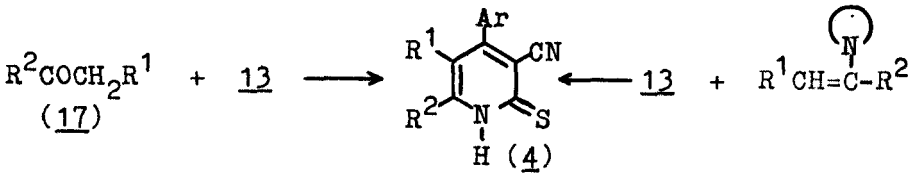


Hydrogenated 3-cyanopyridine-2(1H)-thiones were prepared in a reaction of α,β-unsaturated carbonyl compounds with cyanothioacetamide in ethanol in the presence of equimolar amount of a base at ambient temperature and isolated and characterized as salts [3-9]. Acidification of the salts (14) afforded substituted 3-cyano-3,4-dihydropyridine-2(1H)-thiones (15). They are relatively stable but undergo oxidation in solutions into 3-cyanopyridine-2(1H)-thiones (2) and the respective dipyridyldisulfides (16).

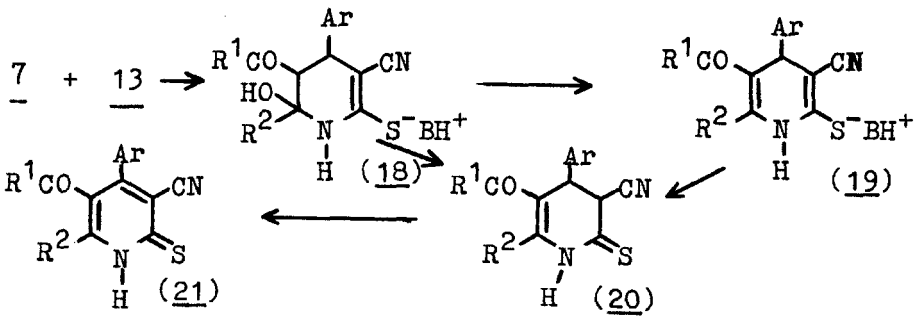


Of wide application in the synthesis of 3-cyanopyridine-2(1H)-thiones and their hydrogenated analogues are reactions of arylidenecyanothioacetamides (13) with α-methylene-

(methyl)carbonyl compounds or the respective enamines. This reaction can be stopped at a stage of either hydrogenated pyridinethiones or pyridine-2(1H)-thiones depending on the structure of the starting carbonyl compound and reaction conditions. Monocarbonyl compounds (17) interact with arylidenecyanothioacetamides (13) to give 3-cyanopyridine-2(1H)-thiones [10-14] whereby, as a rule, no hydrogenated pyridinethiones could be isolated. Analogous results are obtained with enamines, although in these cases the reaction proceeds under milder conditions and in higher yield.



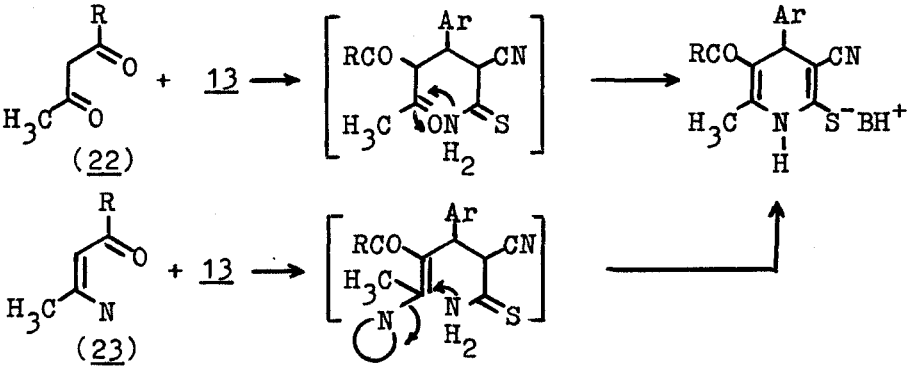
Unlike monocarbonyl compounds, 1,3-dicarbonyl compounds (7) or the respective β-enamines react with arylidenecyanothioacetamides (13) giving rise to hydrogenated 3-cyanopyridine-2(1H)-thiones or their salts [15-22]. In some cases tetrahydropyridine-2-thiolates (18) could be isolated, subsequent dehydration of which results in 3-cyano-1,4-dihydropyridine-2-thiolates (19):



Acidification of the salts (18) or (19) affords 3-cyano-

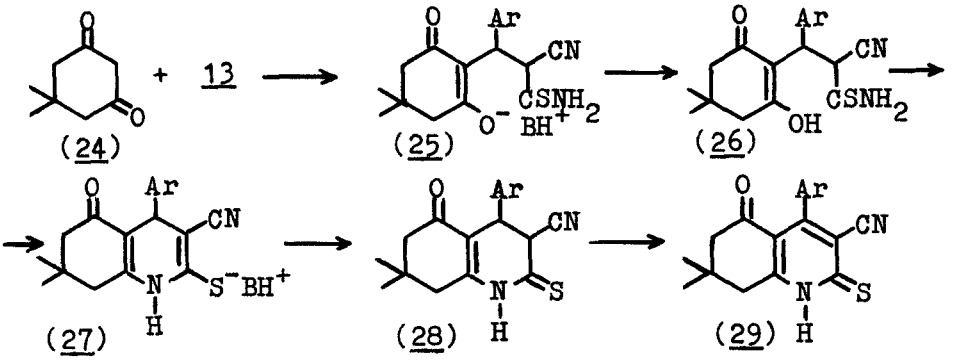
3,4-dihydropyridine-2(1H)-thiones (20) which undergo dehydration in solutions to give, in low yield, pyridine-2(1H)-thiones (21). β-Enaminocarbonyl derivatives, like enamines derived from monocarbonyl compounds, react with arylidenecyanoacetamides (13) in the absence of basic catalysts added and produce higher yields of 1,4-dihydropyridine-2-thiolates.

We have established [22] that reactions of arylidenecyanothioacetamides (13) with nonsymmetrical 1,3-dicarbonyl compounds (22) and enamines (23) derived therefrom are regioselective.

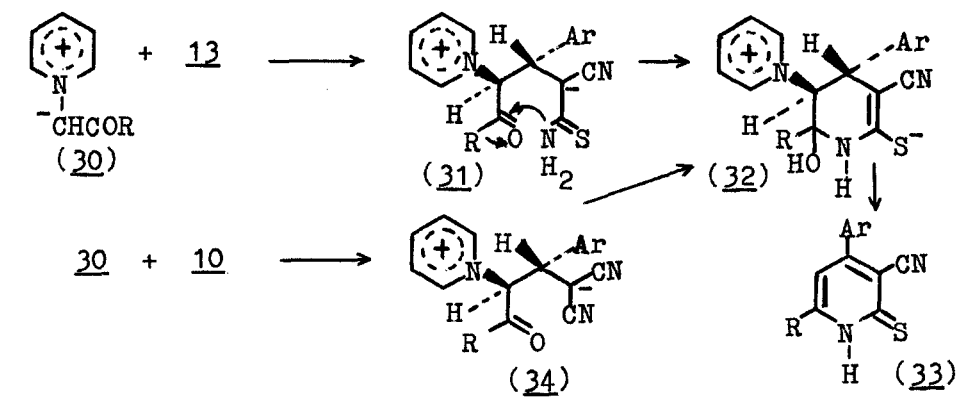


Involvement in the reaction of a cyclic 1,3-dicarbonyl compound, dimedone (24), allowed to shed light on some aspects of the mechanism of this reaction. In particular, Michael adducts were isolated as salts (25) and their properties were investigated. Acidification of the salts (25) results in formation of the adducts (26). Heating of the salts (25) in ethanol or the adducts in the presence of organic bases gives rise to quinoline-2-thiolates (27). The latter are transformed into hydrogenated quinoline-2-thiones (28) on acidification and into quinoline-2(1H)-thiones (29) on heating

in ethanol.



Until recently practically nothing was known on stereochemistry of the reaction of carbonyl compounds with arylidenecyanothioacetamides. We have demonstrated that pyridinium ylides are convenient reagents in the studies of stereochemistry of formation of pyridine-2(1H)-thiones. High stereoselectivity of these reactions was proved to be determined by a stereoselective addition step of pyridinium ylides (30) to arylidenecyanothioacetamides (13) with formation of betaines, 3,4-trans-1,2,3,4-tetrahydropyridine-2-thiolates (32) via intermediates (31). Upon subsequent cyclization of these intermediates (31) into the products (32) the trans-orientation of H-3 and H-4 is retained.

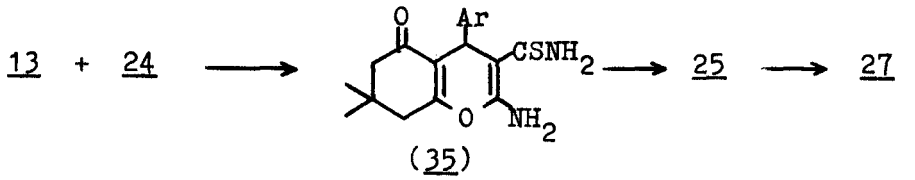


Interaction of arylidenemalononitriles (10) with pyridinium ylides (30) served as a suitable model for the studies of stereochemical aspects of formation of hydrogenated pyridine-2(1H)-thiones. We have demonstrated that the stereoselective formation of products (34) and their stereoselective transformation into betaines (32) upon treatment with hydrogen sulfide is realized in this case as well. The betaines (32) afford pyridine-2(1H)-thiones (33) when heated with ammonium acetate in acetic acid.

Pyridinium ylides were employed also in our studies on mechanism of recyclization of 1,3-dithiacyclohexenes (11) and 4H-thiopyrans (12). These transformations were shown to proceed via arylidenecyanothioacetamides (13) as the common intermediates which react stereoselectively with pyridinium ylides (30) to give 3,4-trans-1,2,3,4-tetrahydropyridine-2-thiolates (32). The latter can smoothly be transformed into pyridine-2(1H)-thiones (33).

We can indicate the following stereoelectronic feature common to 1,3-dithiacyclohexenes (11) and 4H-thiopyrans (12): i) they possess a coplanar enaminonitrile fragment with a highly developed p,π-conjugation system; ii) they are partly hydrogenated; iii) their cycles are sterically overcrowded with bulky electron-acceptor substituents; iv) they are not planar as a whole what results in their thermodynamic instability. On enthalpy rise they cannot lower their energy at the expense of ultimate conformational transitions and undergo cycloelimination at the least strong linka-

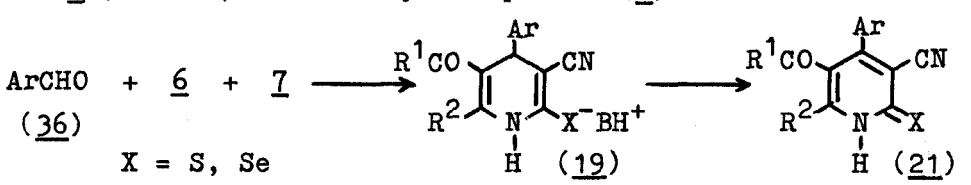
ges. Besides, the transformation products are alike in structure, they possess an exocyclic double bond at position 2. We have established that under conditions of kinetic control arylidenecyanothioacetamides (13) react with dimedone (24) with formation of substituted pyrans (35).



(35)

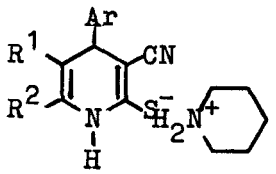
In the presence of bases compounds (35) undergo recyclization to give compounds (25) which, on heating in ethanol, cyclize into quinolinethiolates (27). The latter can be obtained also by a one-pot procedure, without isolation of salts (25), by heating the reagents in ethanol in the presence of bases.

The most attractive, from practical point of view, are the methods of synthesis of substituted 3-cyanopyridine-2(1H)-thiones and -selenones through a three-component condensation of aromatic aldehydes (36), cyanothio(seleno)acetamides (6), and 1,3-dicarbonyl compounds (7).



Conventional dehydrogenation of derivatives (19) gives pyridine-2(1H)-thiones and -selenones (21). Characteristic for this synthetic method is its simplicity, it does not require preliminary preparation of arylidenecyanothio(seleno)-acetamides (13) what could not be realized until recently.

IR-Spectroscopy was used in stereochemical studies of 3-cyanopyridine-2(1H)-thiones, their hydrogenated analogues and salts. Thus, the IR-spectra of pyridinethiones and derivatives (4, 37-39) exhibit adsorption bands of valent vibrations of the cyano group at 2166-2182 cm^{-1} for salts (37), 2200-2203 cm^{-1} for disulfides (38), 2250-2267 cm^{-1} for 3,4-dihydropyridines (39), and 2232-2240 cm^{-1} for pyridinethiones (4). Vibration frequencies for the cyano group increase with decrease in its conjugation within the fragment N-C(S)-C-CN of compounds (4, 37-39).



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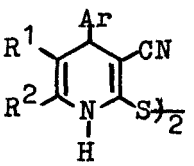

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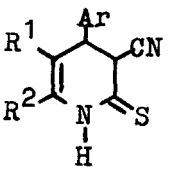
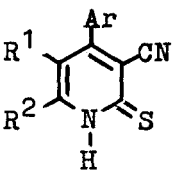
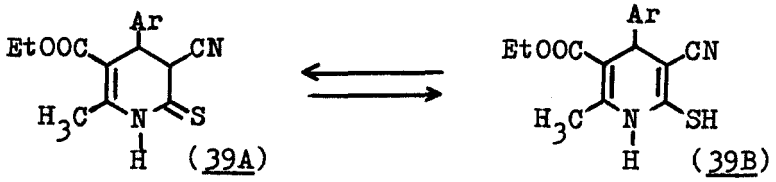


(39)



(4)

Unlike pyridine-2(1H)-thiones (4), hydrogenated 3-cyanopyridine-2(1H)-thiones (39A) are in tautomeric equilibrium, in chloroform solution, with thiols (39B), cis-3,4-dihydropyridine-2(1H)-thiones being to larger extent prone to tautomerization. To estimate the position of tautomeric equilibrium (A ⇄ B), the high-frequency region of the IR-spectra of pyridine-2(1H)-thiones (3150-3300 cm^{-1}), which is characteristic of NH-group adsorption, was analyzed.



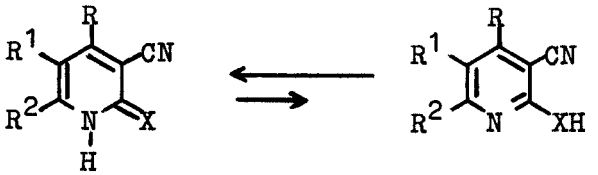
(39A) (39B)

^{1}H and ^{13}C NMR spectroscopy was widely used in structural

Cyanoselenoacetamide (6, X = Se) was obtained by us for the first time by reacting malononitrile with hydrogen selenide [23].

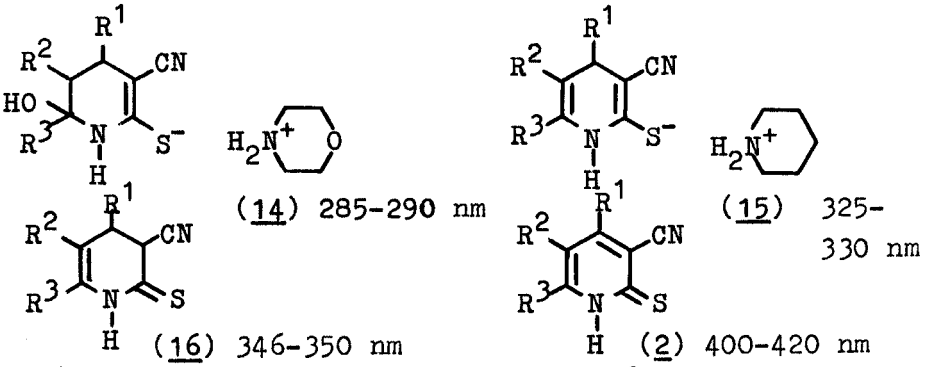
PHYSICO-CHEMICAL PROPERTIES

On the basis of physico-chemical investigations (UV-, IR-, NMR-spectroscopy, mass-spectrometry, X-ray analysis) it was established that 3-cyanopyridine-2(1H)-thiones and -selenones exist preferentially in a thione (selenone) tautomeric form A [1].



(2A) X = S, Se (2B)

Passing to their partially hydrogenated analogues is accompanied by definite changes in their physico-chemical characteristics. Thus, on going from hydrogenated pyridinethiolates (14) to hydrogenated thiones (16), dihydropyridinethiolates (15), and thiones (2) the maxima in their UV-spectra are shifted to longer wavelengths:

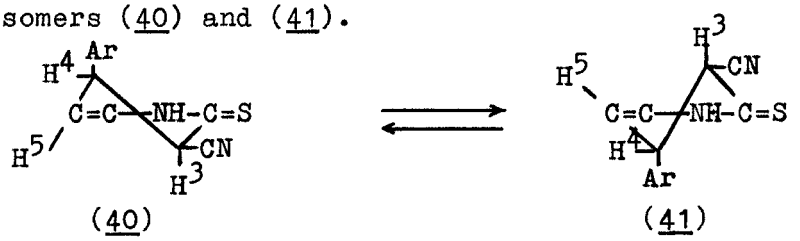


(14) 285-290 nm (15) 325-330 nm

(16) 346-350 nm (2) 400-420 nm

R^1 = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-Py; R^2 = H, COOEt, $COCH_3$; R^3 = Me, Ph

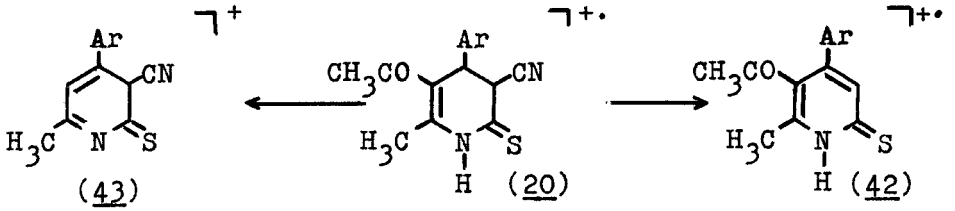
studies of hydrogenated pyridinethiones and their salts. On the basis of ^1H NMR data it was shown that 3,4-dihydropyridine-2(1H)-thiones are mixture of trans- and cis-stereoisomers (40) and (41).



(40) (41)

The $^3J_{3,4}$-value of 11-12 Hz for the isomer (40) points to trans-diaxial orientation of H-3 and H-4 protons. The coupling constant $^3J_{3,4}$ for the cis-isomer (41) was equal to 6 Hz, both isomers being in a dynamic equilibrium. Analogously, NMR spectroscopy has been used in elucidation of spatial structure of 3-cyano-3,4-dihydropyridine-2(1H)-thiones with electron-acceptor groups at position 5.

Electron-impact mass-spectrometry of substituted pyridine-2(1H)-thiones has revealed that they are characterized by high stability (within 24-63% interval). To the contrary, hydrogenated pyridine-2(1H)-thiones (20) exhibit lesser stability towards electron impact (7-8%).



(43) (20) (42)

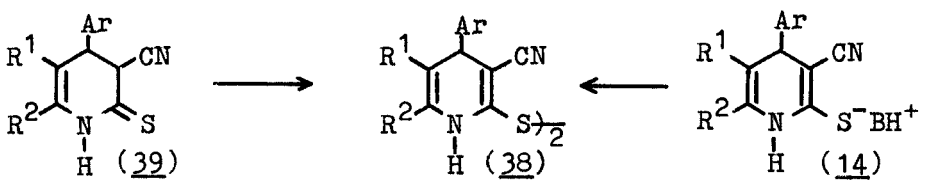
The principal fragmentation processes of molecular ions of hydrogenated pyridinethiones involve competitive elimination of HCN molecule and acyl radical $CH_3CO^{\bullet}$ with formation of tentative structures (42) and (43). Dehydrogenation

processes of pyridinethiones (20) under the action of electron impact are weakly pronounced and the respective peaks constitute about 10% of the molecular ion abundance.

REACTIVITY

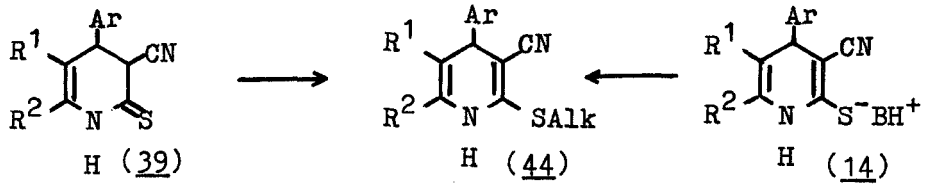
3-Cyanopyridine-2(1H)-thiones and -selenones are bifunctional compounds with two reactive groups: a conjugated cyano group, for which addition reactions are typical, and a thioamide (or selenoamide) group with an endocyclic nitrogen atom, reactivity of which is determined by tautomeric equilibrium, the influence of pyridine ring substituents, and reaction conditions [1].

Typical for 3-cyanopyridine-2(1H)-thiones is their ability to undergo redox reactions at the expense of a thioamide group with an endocyclic nitrogen atom. Hydrogenated pyridine-2(1H)-thiones (39) in solutions are easily oxidized by air oxygen into the corresponding disulfides (38). Preparative synthesis of compounds (38) is effected by treating derivatives (14) or (39) with iodine.

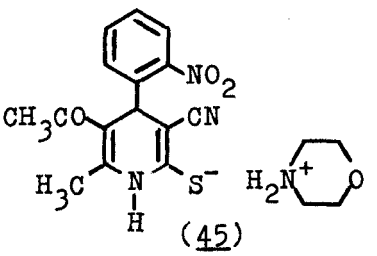


In most details was studied alkylation of 3-cyanopyridine-2(1H)-thiones and -selenones which proceeds with high regioselectivity in the presence of bases to give 2-alkylthio(seleno)pyridines. High regioselectivity was also ob-

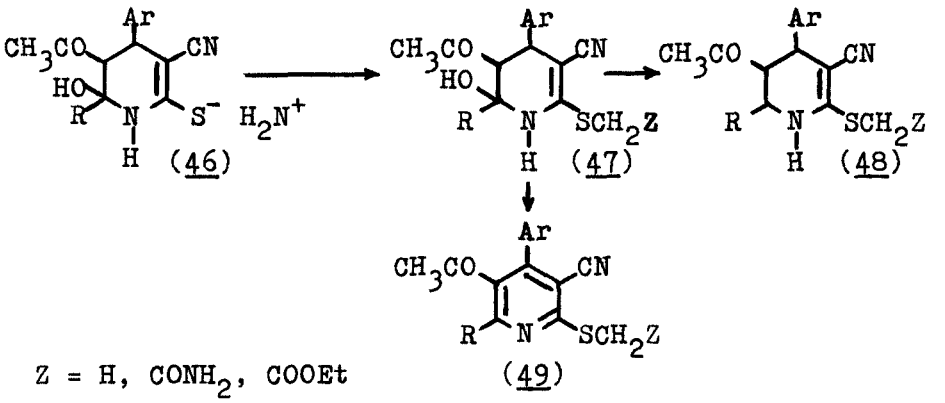
served in alkylation of hydrogenated pyridine-2(1H)-thiones (39) with alkyl halides in basic medium or alkylation of salts (14) to give 2-alkylthio-1,4-dihydropyridines (44).



We have found that partial localization of a negative charge on a sulfur atom is the factor which governs regioselectivity of alkylation of compounds (14). As evidenced from X-ray data, the sulfur atom in pyridinethiolate (45) is, formally, negatively charged.

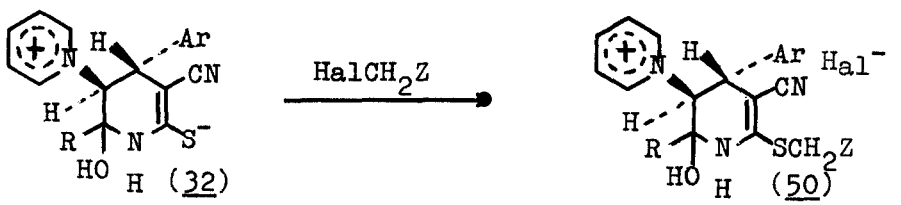


We have also studied alkylation reactions of tetrahydropyridine-2-thiolate salts (46) and directions of dehydration and dehydrogenation of the alkylation products (47). Alkylation of salts (46) was shown to proceed with retention of conformation of the starting compound and formation of 2-alkylthiotetrahydropyridines (47). The latter split a molecule of water off in acidic medium to produce 2-alkylthio-1,4-dihydropyridines (48). In the presence of sodium nitrite aromatization of the heterocycle occurs and 2-alkylthiopyridine (49) is formed.



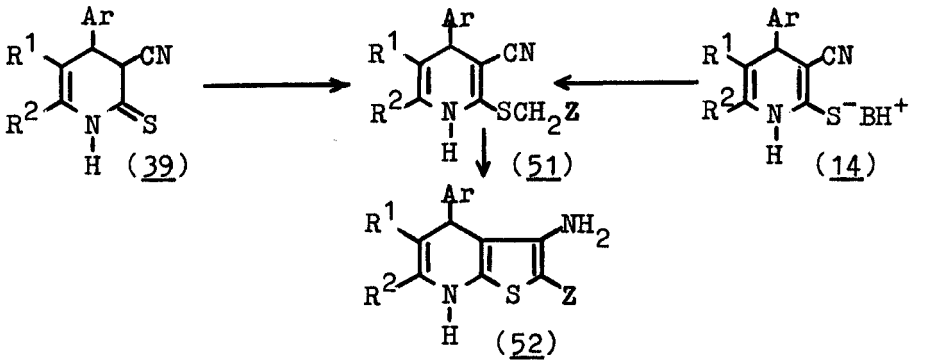
Z = H, $CONH_2$, COOEt (49)

Alkylation of betaines (32) by haloalkanes is also highly regioselective and proceeds with the retention of the original conformation. 6-Alkylthiotetrahydropyridines (50) are formed thereon, trans-pseudodiaxial position of H-3 and H-4 hydrogen atoms and trans-pseudodiequatorial position of substituents Py^+ and Ar being retained.

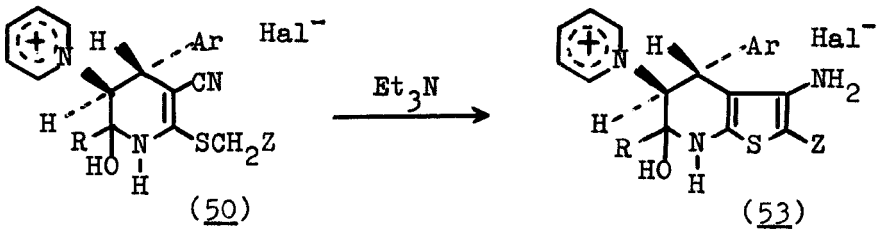


Hal = Cl, Br; Z = H, COAr, $CONH_2$, COOEt

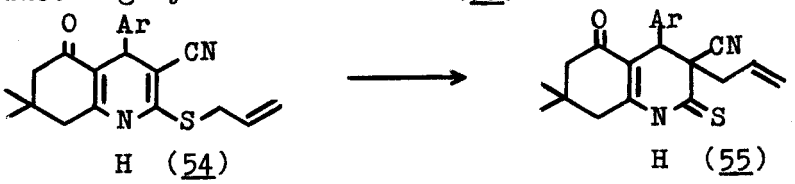
With the use of optical active alkyl halide it was shown that alkylation of pyridine-2(1H)-thiones follows an S_N2 mechanism with Walden inversion at the chiral carbon atom[24]. Relatively high covalent character of sulfur or selenium atoms plays an important role in regioselectivity of alkylation reactions of pyridine-2(1H)-thiones and -selenones. The hydrogenated 2-alkylthio-3-cyanopyridines (39) and salts (14) were employed in the synthesis of 3-aminodihydrothieno[2,3-b]pyridines (52).



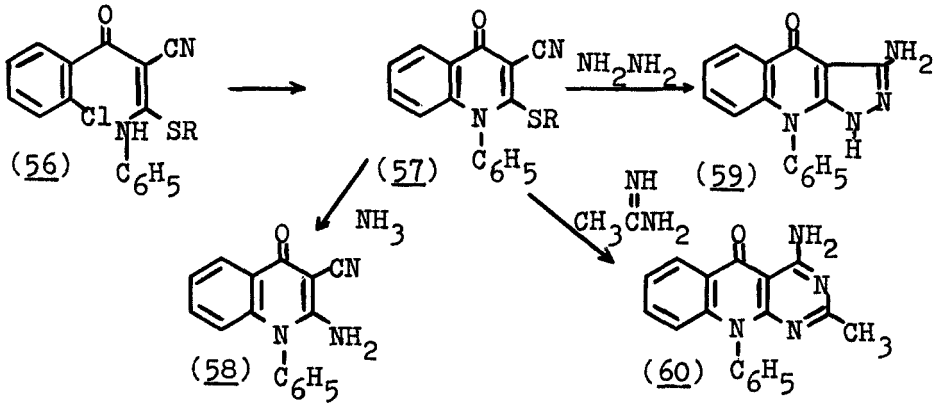
Synthesis of compounds (52) can be effected by a one-pot procedure, without isolation of 2-alkylthiopyridines (51), in the presence of exess of a base. Starting from salts (50) were also synthesised the 3-aminotetrahydrothieno-[2,3-b]pyridines (53). The transoid orientation of the substituents Py^+ and Ar is not changed thereupon.



Unusual was the behaviour of 2-allylthioquinoline (54). Heating of the compound (54) in organic solvents or in solid state results not in its cyclization into thienoquinoline, but in [3,3]-sigmatropic rearrangement with allyl substituent migration into position 3 of the pyridine ring to produce high yield of thiones (55).



A rather peculiar transformation was observed for 3-cyano-2-methylthio-4-oxo-1-phenylquinoline (57) which was obtained from compound (56) by intramolecular condensation [25].



On interaction of the compound (57) with ammonia an amine (58) was isolated. Fused heterocyclic systems (59) and (60) were obtained in a reaction of (57) with hydrazine and acetamidine, respectively [26].

SOME ASPECTS OF PRACTICAL USE

3-Cyanopyridine-2(1H)-thiones and derivatives thereof have found wide application in various areas of fine organic synthesis, in chemistry of dyes, biologically active compounds, and others [1]. Many of 3-cyano-3,4-dihydropyridine-2(1H)-thiones synthesized and their saltsexhibit cardiovascular activity [8,9,27,28].

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REFERENCES

1. V.P.Litvinov, L.A.Rodinovskaya, Yu.A.Sharanin, A.M.Shestopalov, and A.Senning, Sulfur Reports, 1992, in press.
2. J.Pelčer, A.Krauze, Z.Bomika, and G.Dubur, 9th Intern. Symposium on Organic Sulphur Chemistry, Riga, 1980, 136.
3. A.A.Krauze Z.N.Kalme, Yu.E.Pelcher, I.V.Dipan, and G.Ya. Dubur, Khim. Geterotsikl. Soedin., 1983, 1515.
4. A.A.Krauze, E.E.Liepin'sh, Yu.E.Pelcher, Z.N.Kalme, and G.Ya.Dubur, Khim. Geterotsikl. Soedin., 1987, 75.
5. A.A.Krauze, R.O.Vitolinya, G.V.Zarin'sh, Yu.E.Pelcher, Z.A.Kalme, A.A.Kimenis, and G.Ya.Dubur, Khim.-Farnatsevt. Zh., 19, 540 (1985).
6. M.J.Rubio, C.Seoane, J.L.Soto, and A.Susacta, Liebigs Ann. Chem., 1986, 210.
7. A.A.Krauze, E.E.Liepin'sh, Yu.E.Pelcher, and G.Ya.Dubur, Khim. Geterotsikl. Soedin., 1987, 124.
8. A.A.Krauze, R.O.Vitolinya, M.R.Romanova, and G.Ya.Dubur, Khim.-Pharmatsevt. Zh., 22, 548 (1988).
9. A.A.Krauze, R.O.Vitolinya, M.R.Romanova, and G.Ya.Dubur, Khim.-Pharmatsevt. Zh., 22, 855 (1988).
10. V.P.Litvinov, V.K.Promonenkov, Yu.A.Sharanin, A.M.Shestopalov, L.A.Rodinovskaya, V.Yu.Mortikov, and V.S.Bogdanov, Izvestiya Akad. Nauk SSSR, Ser. Khim., 1985, 2101.
11. Yu.A.Sharanin, A.M.Shestopalov, V.P.Litvinov, V.Yu.Mortikov, M.P.Goncharenko, and V.K.Promonenkov, Zh. Org. Khim., 22, 1962 (1986).
12. V.P.Litvinov, Yu.A.Sharanin, L.A.Rodinovskaya, V.Yu. Mortikov, and A.M.Shestopalov, 11th Intern. Symposium

on the Organic Chemistry of Sulfur, Lindau, 1984, 23.
13. V.P.Litvinov, Yu.A.Sharanin, and A.M.Shestopalov, Sulfur Lett., 1985, 99.
14. Yu.A.Sharanin, L.A.Rodinovskaya, V.P.Litvinov, V.K.Promonenkov, V.Yu.Mortikov, and A.M.Shestopalov, Zh. Org. Khim., 21, 683 (1985).
15. J.L.Soto, C.Seoane, M.J.Rubio, and J.M.Botija, Organic preparation and procedures, 16, 11 (1984).
16. L.A.Rodinovskaya, Dissert. Candidat of Sciences, Moscow, 1985.
17. A.A.Krauze, E.E.Liepin'sh, Yu.E.Pelcher, Z.A.Kalme, I.V.Dipan, G.Ya.Dubur, Khim. Geterotsikl. Soedin., 1985, 95.
18. A.A.Krauze, E.E.Liepin'sh, Yu.E.Pelcher, Z.A.Kalme, and G.Ya.Dubur, Khim. Geterotsikl. Soedin., 1986, 630.
19. Yu.A.Sharanin, A.M.Shestopalov, L.A.Rodinovskaya, V.N. Nesterov, V.E.Shklover, V.K.Promonenkov, and V.P.Litvinov, Zh. Org. Khim., 22, 2600 (1986).
20. Yu.A.Sharanin, M.P.Goncharenko, and A.M.Shestopalov, Zh. Org. Khim., 21, 2470 (1985).
21. H.A.Hammouda, A.M.El-Reedy, and S.M.Hussuin, J. Heterocycl. Chem., 23, 1203 (1986).
22. V.P.Litvinov, V.K.Promonenkov, Yu.A.Sharanin, and A.M. Shestopalov, in "Itogi nauki i tekhniki" ("Summary of the Science and Technique"), Ed. M.J.Kabachnik, VINITI, Ser. org. Khim., Moscow, 17, 72 (1989).
23. V.P.Litvinov, V.Yu.Mortikov, Yu.A.Sharanin, and A.M. Shestopalov, Synthesis, 1985, 98.
24. N.Furukawa, T.Kawai, and S.Oae, Synthesis, 1984, 746.
25. W.D.Rudorf, Tetrahedron, 34, 725 (1978).
26. W.D.Rudorf and M.Augustin, J. prakt. Chem., 323, 55 (1981).
27. A.M.Shestopalov, Dissert. Doctor of Sciences, Moscow, 1991.
28. G.Duburs, A.Krauze, and J.Pelcers, 14th Symposium on the Organic Chemistry of Sulfur, Lodz, C-P-5.