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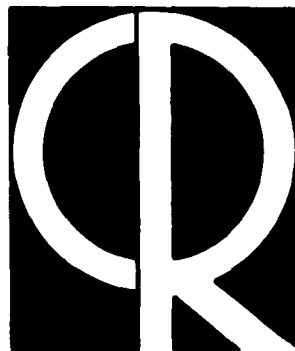
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Research Translation

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Investigations in a Pyridylthiazolymethane Series

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TRANSLATION OF

INVESTIGATIONS IN A
PYRIDYLTHIAZOLYLMETHANE SERIES

(Issledovaniia v riadu piridiltiazolilmetana)

by

V. G. Ermolaeva and M. N. Shchukina

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**INVESTIGATIONS IN A
PYRIDYLTHIAZOLYLMETHANE SERIES**

**I. The Synthesis and Properties of a 4-pyridyl-2'-thiazolylcarbinol.
The Formation of Free Radicals.**

by

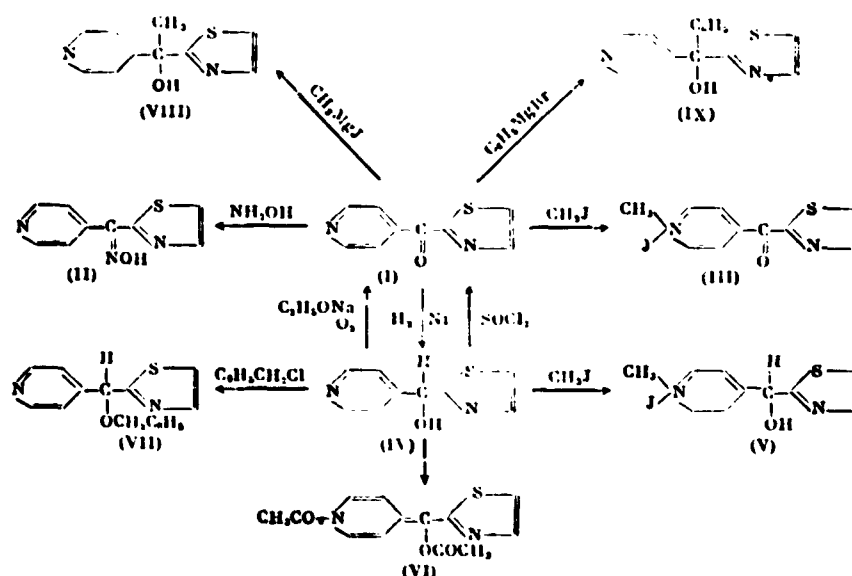
V. G. Ermolaeva and M. N. Shchukina

Derivatives of pyridylthiazolylmethane have been studied very briefly. It is interesting to synthesize them for a search of the physiologically active substances and also to study the effect of the pyridine and thiazol radicals on the chemical properties of such methane substitutes. It also appeared especially interesting to obtain and study the chemical properties of the pyridylthiazolylcarbinols, which can be considered analogous to benzhydrol, whose radical is contained in the structure of a number of highly active substances.

4-pyridyl-2'-thiazolylcarbinol (IV) was obtained by hydrogenation of the 4-pyridyl-2'-thiazolylketone (I) in the presence of Reney's nickel. The initial 4-pyridyl-2'-thiazolylketone was derived from 2-bromothiazol and an ethyl ether of isonicotinic acid by lithium-organic synthesis with a 55% yield and was characterized by obtaining hydrochloride, oxime (II) and iodomethylate (III) from it. The hydrogenation of a ketone takes place rapidly at room temperature, a theoretical amount of hydrogen being absorbed. 4-pyridyl-2'-thiazolylcarbinol is a crystalline substance whose structure is

revealed by elementary analysis; the presence of a hydroxyl group is revealed by determining a hydroxyl, according to Tserevitinov, and also by comparing the UV absorption spectra with the spectra of the phenylthiazolylcarbinol and of tertiary methyl-4-pyridyl-2'-thiazolylcarbinol (VIII) and phenyl-4-pyridyl-2'-thiazolylcarbinol (IX) (figure 1). The latter were obtained from the 4-pyridyl-2'-thiazolylketone (I) by magnesium organic synthesis when using 2-multiple portions of the Grignard reagents.

In spite of the production methods and the fact that elementary analysis and UV spectrum data completely reveal the structure of the 4-pyridyl-2'-thiazolylcarbinol, this combination behaves unusually in a number of reactions for secondary carbinols. When an acetic anhydride reacts in cold, a yellow diacetyl derivative forms; its structure (VI) is given here.



The diacetate formation (VI) can be explained by the regrouping of hydrogen from the methane carbon to the nitrogen of the pyridine ring and by the ensuing acetylation. A second possibility - regrouping to the nitrogen of the thiazol ring - is less probable, since this atom has a weak electro-negative nature due to the effect of the sulfur atom and the hydrogen of the hydroxyl group. The inability of methane hydrogen to regroup to the nitrogen of the thiazol is also confirmed by the fact that the phenylthiazolylcarbinol only yields a monoacetyl derivative (figure 2), whose UV spectrum agrees with the UV spectrum of phenyl-2-thiazolylcarbinol, as well as with the spectra of 4-pyridyl-2'-thiazolylcarbinol and tertiary phenyl-4-pyridyl-2'-thiazolyl (IX) and the methyl-4-pyridyl-2'-thiazolylcarbinols (VIII) and sharply differs from the UV spectrum of the diacetyl derivative of the 4-pyridyl-2'-thiazolylcarbinol (VI). The latter compound is yellow and its absorption spectrum tends toward longer waves, which corresponds to an extension of the polarized conjugate system of double bonds.

The behavior of 4-pyridyl-2'-thiazolylcarbinol (IV) was unusual with respect to thionylchloride. The reaction takes place without yielding hydrogen chloride and sulfur dioxide, and after treating with water it begins to form a ketone chlorine hydrate. In this case, the thionylchloride behaves according to the type of radical reactions in the same way it does when it reacts with phenoxazine, for example.¹

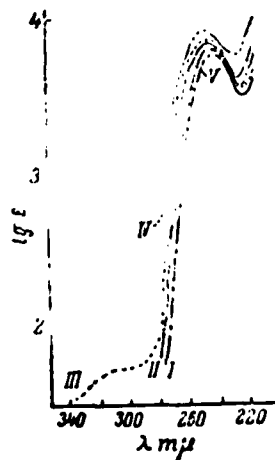


Figure 1. UV spectra of absorption.

- I: phenyl-2-thiazolylcarbinol;
- II: methyl-4-pyridyl-2'-thiazolylcarbinol;
- III: 4-pyridyl-2'-thiazolylcarbinol;
- IV: phenyl-4-pyridyl-2'-thiazolylcarbinol;
- V: o-acetylphenyl-2-thiazolylcarbinol.

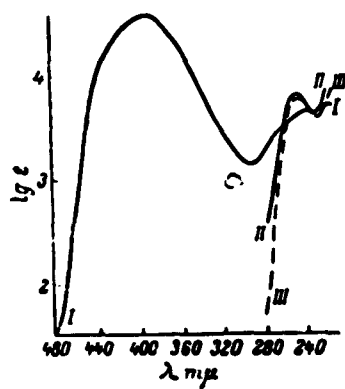


Figure 2. UV spectra of absorption.

- I: a diacetyl derivative of 4-pyridyl-2'-thiazolylcarbinol;
- II: o-acetylphenyl-2-thiazolylcarbinol;
- III: phenyl-2-thiazolylcarbinol.

The tendency of 4-pyridyl-2'-thiazolylcarbinol (IV) toward radical conversions is very evident when it reacts with an alcohol sodium alcoholate solution. In this case, intensely blue solutions form which, when shaken with air, rapidly become colorless; when they set for several seconds, they again turn blue (jet-red iron blue), becoming colorless again after repeated shaking. This appearance and disappearance of color will occur 15 - 20 times and reminds one of the Schmidlin phenomenon which occurs with a benzene solution of hexaphenylethane.² A peroxide compound forms in the colorless solution which breaks down into sodium peroxide (0.5 g mol per 1 g mol of 4-pyridyl-2'-thiazolylcarbinol); an equivalent amount of 4-pyridyl-2'-thiazolylketone which was separated and identified also forms. The intensely blue solution, which forms when a small amount of 4-pyridyl-2'-thiazolylcarbinol is dissolved in an alcohol alcoholate solution, becomes colorless when cooled below -5° ; the intensely blue color reappears when it is heated above 0° . After the blue solution is acidified to a pH of 6.5 - 7.5, the unchanged 4-pyridyl-2-thiazolylcarbinol (IV) is separated with an almost theoretical yield. When a dry carbonic anhydride passes through a dark blue solution of carbinolate, a colorless unwieldy precipitate forms; when this is treated with water, the unchanged carbinol (IV) also precipitates. It is difficult for a dark blue carbinol solution to react with the alkyl halides. Sodium chloride can be separated only when heated with benzyl chloride, and the yield of o-benzyl-4-pyridyl-2-thiazolylcarbinol (VII) is small; but when heated with methyl iodide

in the presence of air only the 4-pyridyl-2'-thiazolylketone (I) was obtained; this indicates that the formation of radicals and the ensuing acidification take place more rapidly than alkylation. From the data given, it can be concluded that sodium 4-pyridyl-2'-thiazolylcarbinolate in an alcohol solution is subject to oxidation with an intermediate formation of a stable radical which is obviously similar to the metal-ketones which form when sodium reacts in ether solutions of the aromatic and ditertiary ketones.³ The radical breakdown of sodium 4-pyridyl-2'-thiazolylcarbinolate obviously is caused by the strong electronegative nature of the substitutes in the central methane atom of carbon and by the effect of the γ -nitrogen of the pyridine ring.

The electron paramagnetic resonance spectrum (EPR) (figure 3) verified the presence of radicals in a solution of sodium 4-pyridyl-2'-thiazolylcarbinolate. From the structure of the EPR spectrum, it can be concluded that free radicals, possibly the hepta-quinoid type, occur in the solution and that the odd electron of the free radical is delocalized with respect to both nuclei and reacts with the seven protons. In the colorless solution which results from shaking with air, the radicals disappear and reappear depending on the intensity of the blue color, i. e. , the concentration of radicals is determined by the concentration of the colored substances.

The formation of the colored radical in a sodium 4-pyridyl-2'-thiazolylcarbinolate solution is connected with the presence of hydrogen near the carbon of the secondary alcohol group, since the tertiary phenyl-4-pyridyl-2'-thiazolyl- (IX) and methyl-4-pyridyl-

2'-thiazolylcarbinols (VIII) do not form such solutions.

Concerning the effect of the γ -pyridine radical on the tendency toward radical breakdown, on the basis of the fact that free-radical formation was not observed for phenyl-2-thiazolylcarbinol, it can be affirmed with certainty that its solutions are colorless in an alcohol sodium alcoholate and are stable in air.

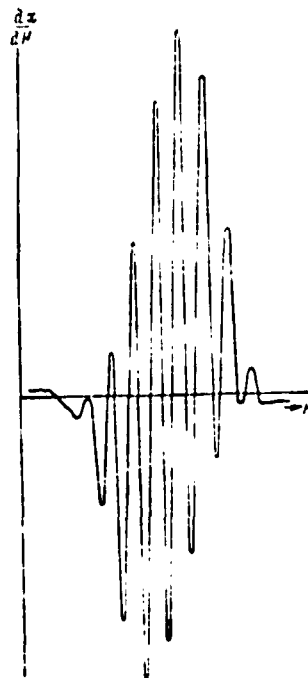


Figure 3. EPR spectrum of a sodium 4-pyridyl-2'-thiazolylcarbinolate solution in ethanol.

In a reaction of 4-pyridyl-2'-thiazolylcarbinol with methyl iodide in a methylethylketone solution, the latter is connected with the formation of monoiodomethylate (V). Obviously, the methyl iodide

joins only the pyridine nitrogen. The iodomethylate of 4-pyridyl-2'-thiazolylcarbinol (V) is also subject to radical breakdown in alkaline solutions, and the radical which forms in the dark blue-green solution oxidizes even more rapidly when the solution is shaken with air, in this case converting to the iodomethylate of 4-pyridyl-2'-thiazolylketone (III).

Experimental Part *

2-bromothiazol was obtained from 2-aminothiazol according to the Ganapathy and Venkataraman method⁴ with about a 71.5% yield; the boiling point was 54 - 55° at 9 mm.

4-pyridyl-2'-thiazolylketone (I). Add 71.5 grams of butyl chloride in a 200 ml solution of dry ether to 12.5 grams of finely cut lithium in 300 ml of absolute ether very gradually at a temperature of -10°; then agitate the mixture for two hours at -10° to 0°; cool to -45° and gradually add a solution of 95 grams of 2-bromothiazol in 120 ml of absolute ether.⁵ Mix the reaction mass at this temperature for 45 minutes, then raise the temperature to -30°, and gradually add a solution of 90 grams of distilled ethyl ether of isonicotinic acid in 100 ml of absolute ether, mixing for 1 hour at -30°, then 30 minutes at -15°; then when cooling, gradually pour through a sieve into 600 ml of cooled, diluted (1 : 3) hydrochloric acid. The ether layer is separated and extracted twice by the diluted acid. After purifying the acid extracts with carbon, treat

* The EPR spectrum was taken by L. A. Bliumenfeld and A. E. Kalmanson, the UV spectrum by E. M. Peresleni, to whom we express many thanks.

them with an aqueous ammonia solution when cooling to -5° .

The precipitate which has been separated is then recrystallized.

The yield is 61 grams (55%). The aciculae are colorless; melting point -- 117° - 118° (in alcohol). They are soluble in alcohol, hot water; more difficult in ether, benzene.

Percentage yield: C 56.60; H 3.11; N 14.89; S 16.72
 $C_9H_6N_2OS$.

Percentage calculated: C 56.67; H 3.18; N 14.73; S 16.86.

A chlorine hydrate is obtained by adding an alcohol solution of hydrogen chloride to the solution of the base in ether. The light yellow aciculae have a melting point of 203° - 204° . They dissolve easily in water and hot alcohol.

Percentage yield: C 47.64; H 3.65; N 11.85; Cl 15.78.
 $C_9H_6N_2OS \cdot HCl$.

Percentage calculated: C 47.67; H 3.11; N 12.36; Cl 15.64.

Oxime (II): Add an aqueous solution of 0.18 g of hydrochloric hydroxylamine and 0.1 g of solid caustic soda to 0.5 g of the ketone dissolved in alcohol. Filter off the sodium chloride precipitate and boil the solution for two hours. Filter off again the precipitate, wash with 50% hot alcohol and recrystallize in alcohol. The white crystals have a melting point of 218° - 219° (ground).

Percentage yield: C 52.53; H 3.58; N 20.50; S 15.77.
 $C_9H_7N_3OS$.

Percentage calculated: C 52.66; H 3.41; N 20.45; S 15.63.

Iodomethylate (III). Heat a solution of 2 g of 4-pyridyl-2'-thiazolylketone (I) in 15 ml of methylethylketone for 30 minutes with

5 ml of methyl iodide. Filter off the precipitate and wash with ether. Weight is 3.66 g. The orange crystals have a melting point of 204° - 206° (in alcohol).

Percentage yield: C 35.94; H 2.65; N 8.59; J 37.76;
C₁₀H₉JN₂OS.

Percentage calculated: C 36.15; H 2.73; N 8.43; J 38.20.

4-pyridyl-2'-thiazolylcarbinol (IV). Hydrogenate a solution of 10 grams of 4-pyridyl-2'-thiazolylketone (I) in 300 ml of dry alcohol over Reney nickel at room temperature and atmospheric pressure, whereupon an almost theoretical amount of hydrogen is absorbed. After removing the catalyzer and treating with carbon, evaporate the solution in a vacuum. Recrystallize the precipitate (9.8 g). The white crystals have a melting point of 132° - 134° (in alcohol). They dissolve in alcohol, but with more difficulty in water.

Percentage yield: C 56.39; H 4.20; N 14.61; S 16.58; OH 9.17
C₉H₈N₂OS.

Percentage calculated: C 56.24; H 4.19; N 14.57; S 16.68;
OH 8.86.

The solute readily dissolves in hydrous alkalines to form a light green solution. It dissolves in an alcohol sodium alcoholate solution, forming a bright blue (jet-red iron blue) solution. When the freezing mixture is cooled from -5° to -7°, the blue color of the dilute solutions disappears, and then reappears when heated to room temperature. When heated in a water bath, dilute solutions gradually become colorless. When these blue solutions are shaken with air, the color disappears and again reappears after setting several seconds.

After repeated shakings (up to 20), the color no longer appears.

Add 0.1234 g (0.00064 g mol) of 4-pyridyl-2-thiazolylcarbinol (IV) to a 5 ml alcohol solution of 0.02 g of sodium; shake the obtained intensely blue solution until the color no longer appears. Then add a water solution of 0.15 g of sodium iodide, acidify with HCl and titrate the iodine which is separated with 3.1 ml of a 0.1 N solution of sodium thiosulfate, which corresponds to a 0.00031 gram equivalent of the hydrogen peroxide which is formed. Treat the solution with ammonia, extract with ether, then dry and remove the solvent. The 0.11 g yield has a melting point of 113° - 114°; no depression is caused in a sample mixed with 4-pyridyl-2-thiazolylketone (I).

A hydrochloride is obtained by adding an alcohol solution of a hydrogen chlorate to an alcohol solution of 4-pyridyl-2-thiazolylcarbinol (IV). The light yellow crystals have a melting point of 182° - 184° (in alcohol). They decompose rapidly.

Percentage yield: C 47.08; H 4.07; N 12.01; S 15.90.
C₉H₈N₂O₂S · HCl.

Percentage calculated: C 47.26; H 3.97; N 12.26; S 15.50.

Iodomethylate (V): Boil for three hours a mixture of 1 gram of 4-pyridyl-2-thiazolylcarbinol (IV), 10 ml of methylethylketone and 3 ml of methyl iodide, thus recrystallizing the light yellow precipitate (1.67 g) which has been separated. These light yellow crystals have a melting point of 187° - 189° (in anhydrous alcohol). They dissolve in water and alcohol.

Percentage yield: C 35.85; H 3.21; N 8.00; J 37.76.
 $C_9H_8N_2OS \cdot CH_3J$.

Percentage calculated: C 35.93; H 3.32; N 8.38; J 37.97.

These crystals dissolve in dilute ammonia and in alcohol alcoholate, forming dark blue-green solutions which become colorless when shaken, setting, or heated. The iodomethylate (III), which is identical with that obtained from ketone (I), precipitates from the colorless alcohol solutions.

Acetylation of 4-pyridyl-2'-thiazolylcarbinol: Leave a mixture of 1.6 g of carbinol with 1.1 g of anhydrous sodium acetate and 25 ml of acetic anhydride overnight. Then pour in 100 ml of water, heating slightly to decompose the acetic anhydride, and filter off the precipitated yellow substance (VI). The yield is 1.4 grams. The shiny yellow flakes have a melting point of $127^\circ - 128.5^\circ$ (in 50% alcohol).

Percentage yield: C 56.49; H 4.45; N 10.03; S 11.67.
 $C_{13}H_{12}N_2O_3S$.

Percentage calculated: C 56.50; H 4.35; N 10.15; S 11.60.

o-Acetylphenyl-2-thiazolylcarbinol. Leave a mixture of 3.6 grams of phenyl-2-thiazolylcarbinol, 40 ml of acetic anhydride and 1.7 grams of anhydrous sodium acetate overnight; then proceed as above. Extract the separated oil with ether, and dry over tempered magnesium sulfate. Drive off the ether and distill the precipitate in a vacuum. The 2.5 g yield has a boiling point of $153^\circ - 154^\circ$ at 2 mm.

Percentage yield: C 61.63; H 4.62; N 6.23; S 13.67.
 $C_{12}H_{11}NO_2S$.

Percentage calculated: C 61.77; H 4.72; N 6.77; S 13.74.

The reaction of 4-pyridyl-2-thiazolylcarbinol (IV) with thionyl chloride. Add 3 ml of freshly distilled thionyl chloride to 1 gram of carbinol (IV) suspended in 30 ml of anhydrous chloroform at -10° . The mixture turns reddish brown; the hydrogen chloride and sulfur dioxide do not pass off. Let the mixture stand overnight, distill off the thionyl chloride and chloroform, dissolve the residue in water, treat with carbon and alkalize with ammonia to a pH of 8 - 8.5. Filter off and recrystallize the precipitate (0.6). The melting point is 114° - 115° (in alcohol). No depression is produced with ketone (I) in the mixture sample.

Methyl-4-pyridyl-2-thiazolylcarbinol (VIII). Add gradually a solution of 9.5 grams of ketone (I) in 400 ml of absolute ether to Grignard's reagent (14.5 g of methyl iodide and 2.53 g of magnesium in 50 ml of ether) when cooling with water. Heat the brownish-red reaction mass for 2.5 hours at the boiling point for ether, then cool it, adding an ammonium sulfate solution, and extract with ether. Boil off the ether, and recrystallize the residue (8.5 g). The yield is 6.1 grams (68%); the white crystals have a melting point of 173° - 174° (in alcohol). The carbinol (VIII) solution is colorless in an alcohol sodium alcoholate.

Percentage yield: C 58.04; H 4.89; N 13.28; S 15.13.
 $C_{10}H_{10}N_2OS$.

Percentage calculated: C 58.22; H 4.88; N 13.58; S 15.57.

Iodomethylate is obtained similarly (V). The white crystals, which turn yellow quickly, have a melting point of 217° - 218° (in alcohol).

Percentage yield: C 38.15, H 3.94; N 8.19; J 36.37.
C₁₁H₁₃N₂OS.

Percentage calculated: C 37.93; H 3.76; N 8.05; J 36.44.

Phenyl-4-pyridyl-2'-thiazolylcarbinol (IX). Add gradually a solution of 9.5 g of ketone (I) in 400 ml of absolute ether to Grignard's reagent (2.4 g of magnesium and 16 g of brombenzene in ether) when cooling with water. Heat the reaction mass for three hours at the boiling point for ether, then cool it; add an aqueous solution of ammonium sulfate, and extract with ether. Boil off the ether and recrystallize the residue. The white crystals have a melting point of 211.5° - 212.5° (in alcohol). The yield is 74.5%. The carbinol (IX) solution is colorless in an alcohol sodium alcoholate.

Percentage yield: C 67.34; H 4.47; N 10.42; S 11.66.
C₁₅H₁₂N₂OS.

Percentage calculated: C 67.17; H 4.51; N 10.45; S 11.94.

o-Benzyl-4-pyridyl-2'-thiazolylcarbinol (VII). Add a solution of 2.26 g of carbinol (IV) in 20 ml of alcohol to a sodium alcoholate (0.25 g of sodium and 10 ml of anhydrous alcohol) cooled to 5°. Mix the dark blue solution at room temperature for 1 hour; add 1.6 g of benzyl chloride in 5 ml of alcohol and boil 3 hours. Then cool, filter the precipitate and recrystallize it. The yield is 1 gram and the melting point is 212° - 213° (in chloroform).

Percentage yield: C 67.51; H 5.05; N 9.71; S 10.31.
 $C_{16}H_{14}N_2O_2S$.

Percentage calculated: C 68.10; H 4.905; N 9.93; S 11.36.

CONCLUSIONS

1. Catalytic hydrogenation of 4-pyridyl-2'-thiazolylketone, which is synthesized from the ethyl ether of isonicotinic acid and 2-lithiumthiazol, yielded the 4-pyridyl-2'-thiazolylcarbinol; its structure was revealed by UV spectra analyses, and by their comparison with the spectra of the phenyl-2-thiazolylcarbinol and the tertiary phenyl-4-pyridyl-2'-thiazolyl- and methyl-4-pyridyl-2'-thiazolyl-carbinols.

2. Analysis of the chemical properties of 4-pyridyl-2-thiazolyl carbinol showed that

- (a) during an acetic anhydride reaction, prototropic regrouping of hydrogen from methane carbon to the nitrogen of the pyridine nucleus takes place and a diacetyl derivative forms;
- (b) in alkaline and sodium alcoholate solutions, 4-pyridyl-2'-thiazolylcarbinol forms stable, colored free radicals;
- (c) the radical nature of the 4-pyridyl-2'-thiazolylcarbinolate conversion is an easy proof of its acidification by atmospheric oxygen forming a peroxide (the Schmidlin effect), by the fact that a relationship exists between the degree of dissociation and temperature and by the EPR spectrum;

(d) the iodomethylate of 4-pyridyl-2'-thiazolylcarbinol also forms radicals, producing intensely colored solutions in aqueous alkalies, ammonia and in alcohol sodium alcoholate solutions. These solutions are quickly acidified by atmospheric oxygen forming the iodomethylate of the 4-pyridyl-2'-thiazolylketone and an alkali metal peroxide.

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