with mp 190-193°C (from methanol), in 40% yield. Found: C 68.7; H 5.1; Cl 5.7%. $C_{35}H_{30}ClN_3O_5$. Calculated: C 69.1; H 5.0; Cl 5.8%. IR spectrum: 1100, 1575, 1605, 1630, 1735 cm^{-1}.

1-(5-Tetrazolyl)-2,4,6-triphenylpyridinium Ylid (XI). A suspension of perchlorate X was refluxed briefly in water, after which it was worked up to give betaine XI, with mp 274-275°C (from ethanol), in 88% yield. Found: C 76.7; H 4.9; N 18.7%. $C_{24}H_{17}N_5$. Calculated: C 76.8; H 4.6; N 18.7%. IR spectrum: 1560, 1620 cm^{-1}.

1-(2-Benzimidazolyl)-2,4,6-triphenylpyridinium Ylid (XII). A mixture of perchlorate VIIIg and an equivalent amount of methanolic KOH was refluxed for 30 min, after which it was cooled, and the $KClO_4$ was removed by filtration. The filtrate was evaporated, and the dry residue was recrystallized successively from aqueous methanol and benzene to give the orange-red betaine, with mp 149-150°C, in 96% yield. Found: C 82.1; H 5.7%. $C_{30}H_{21}N_3 \cdot H_2O$. Calculated: C 81.6; H 5.3%. IR spectrum: 1563, 1605, 1630 cm^{-1}.

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REACTION OF PENTACHLOROPYRIDINE WITH SODIOACETOACETIC ESTER

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Ethyl tetrachloro-4-pyridylacetoacetates and tetrachloro-2-pyridylacetoacetates were synthesized by reaction of pentachloropyridine with sodioacetoacetic ester. Hydrolysis of ethyl tetrachloro-2-pyridylacetoacetate gives 3,4,5,6-tetrachloro-2-pyridylacetic acid rather than the corresponding acetone derivative.

Continuing our study of the reactions of pentachloropyridine with carbanions [1, 6], we investigated the reaction of pentachloropyridine with sodioacetoacetic ester. In ethanol this reaction leads to the formation of ethyl 2,3,5,6-tetrachloro-4-pyridylacetoacetate (I) (60%) and 4-ethoxy-2,3,5,6-tetrachloropyridine (20%). According to the results of gas–liquid chromatography (GLC), ethyl 3,4,5,6-tetrachloro-2-pyridylacetoacetate (II) (65%) is primarily obtained in dioxane, along with ester I (20%).

The observed differences are explained by increased dissociation of the sodioacetoacetic ester in alcohol, owing to which the carbanion attacks the 4 position, which is most sensitive to nucleophiles. Alcohol

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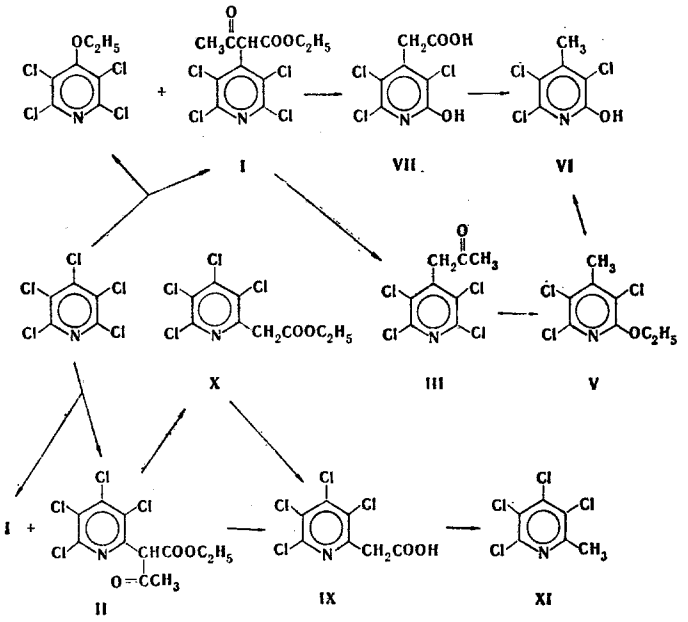
assists detachment of a chloride ion because of specific solvation of this ion. Sodioacetoacetic ester is less dissociated in dioxane, by virtue of which pentachloropyridine is coordinated with sodioacetoacetic ester at the nitrogen atom. The complex, in which the sodioacetoacetic ester is in direct proximity to the chlorine atom in the 2 position, undergoes decomposition to give ester II.

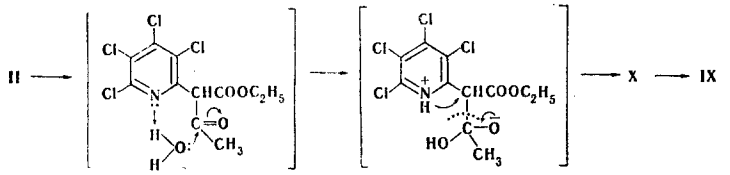


Two bands with successively increasing intensity at 1610 and 1566 cm^{-1} (C=C and C=O stretching vibrations) are observed in the IR spectra of esters I and II. The IR spectrum of ester II contains a broad diffuse band at 2800-3000 cm^{-1}, which does not vanish when the solution is diluted; this constitutes evidence for an intramolecular hydrogen bond (IHB). A broad singlet at 13.4 ppm, which is related to an "enol" proton included in a chelate ring, is observed in the PMR spectra of esters I and II. It is apparent from these data that both esters exist in both ketone and enol forms, although the introduction of a tetrachloropyridyl group promotes a shift in the equilibrium to favor the enol form. Quantitative determination [3] by a bromometric method shows that ester I contains 20% enol and that ester II contains 67% of the enol form. The increased percentage of the enol form in ester II can be explained by the closeness of the hydroxyl group of the enol to the nitrogen heteroatom and the possibility of the formation of a six-membered complex due to an IHB between them.

The action of 80% sulfuric acid on ester I gave 4-acetonyl-2,3,5,6-tetrachloropyridine (III), which was converted to 2,3,5,6-tetrachloroisonicotinic acid (IV) by oxidation with potassium permanganate. When III is heated with sodium ethoxide, not only is the acetyl group detached, but the chlorine atom undergoes nucleophilic substitution by an ethoxy group to give 2-ethoxy-4-methyl-3,5,6-trichloropyridine (V), which was obtained [1] by reaction of 4-methyl-2,3,5,6-tetrachloropyridine with sodium ethoxide. The ethoxy group in V is readily saponified by 80% sulfuric acid to a hydroxy group to give 2-hydroxy-4-methyl-3,5,6-trichloropyridine (VI).

In addition to splitting out of an acetyl group, replacement of the chlorine atom in the 2 position by a hydroxy group to give 2-hydroxy-3,5,6-trichloro-4-pyridylacetic acid (VII) was observed in the reaction of ester I with 25% potassium hydroxide. This was proved by decarboxylation to VI. Transesterification of ester I to the corresponding 2,3,5,6-tetrachloro-4-pyridylacetoacetic esters (VIIIa, b) occurs in the reaction of ester I with concentrated hydrochloric acid in n-butyl or n-heptyl alcohol.

The hydrolysis of ester II proceeds anomalously in both sulfuric acid and aqueous alkali. Thus heating ester II in 80% sulfuric acid does not give the expected acetonyl derivative but rather 3,4,5,6-tetrachloro-2-pyridylacetic acid (IX) in quantitative yield; acid IX is also obtained by the action of 2% aqueous sodium hydroxide on ester II at room temperature. The anomalous behavior of ester II on reaction with sulfuric acid can be explained by the closeness of the carbonyl group of ester II to the nitrogen heteroatom of the pyridine ring. Owing to this, the incorporation of a water molecule between the electrophilic carbon atom of the carbonyl group and the nitrogen atom is possible during hydrolysis, as a result of which an intermediate six-membered complex is formed.



We isolated an intermediate hydrolysis product – ethyl 3,4,5,6-tetrachloro-2-pyridylacetate (X), which is formed by the action of 80% sulfuric acid on ester II at room temperature. Subsequent acid hydrolysis of ester X to acid IX occurs at 115°C, i.e., under the same conditions as in the hydrolysis of ester II. The somewhat increased pK_a value of 3.54 for acid IX as compared with 2,3,5,6-tetrachloro-4-pyridylacetic acid (pK_a 3.23; σ^* 2.31) [1] is evidently explained by the formation of an IHB (IR spectrum 2700-3200 cm^{-1}) between the nitrogen heteroatom and the hydrogen atom of the hydroxyl group. The σ^* inductive parameter of the 3,4,5,6-tetrachloropyridyl residue calculated from the Taft equation [4] is 1.82. With respect to the strength of the –I effect and its ability to shift the keto-enol equilibrium to favor the enol, the tetrachloropyridyl group is comparable to trifluoromethyl, carbomethoxy, and 2,4-dinitrophenyl groups [5, 6].

Acid IX undergoes decarboxylation at 170°C to give 2-methyl-3,4,5,6-tetrachloropyridine (XI), which was oxidized to 3,4,5,6-tetrachloropicolinic acid (XII) with potassium permanganate. The formation of the described acids IV and XII [2, 7] proves the site of substitution of chlorine by an acetoacetic ester residue.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Tesla BS-487B spectrometer at room temperature with hexamethyldisiloxane as the external standard. The IR spectra of CCl_4 solutions of the compounds were recorded with a UR-20 spectrometer. Analysis by GLC was carried out with a Tsvet-3 chomatograph with SE-30 siloxane polymer applied to Chromosorb W-HMDS.

Ethyl 2,3,5,6-tetrachloro-4-pyridylacetoacetate (I). A 32.5-g (0.25 mole) sample of acetoacetic ester was added dropwise to 0.46 g (0.2 g-atom) of sodium in 200 ml of ethanol, 25 g (0.1 mole) of pentachloropyridine was added, and the mixture was refluxed with stirring for 6 h. The alcohol was then removed by vacuum distillation, and the residue was treated with 1% NaOH. The undissolved oil was separated, the solution was acidified with concentrated HCl, and the precipitated ester I was removed by filtration.

The oil, which was insoluble in aqueous alkali, was vacuum distilled to give 4.8 g (20%) of 4-ethoxy-2,3,5,6-tetrachloropyridine with bp 140-141°C (5 mm) and mp 57-58°C (from ethanol) (mp 58-59°C) [1].

Ethyl 3,4,5,6-Tetrachloro-2-pyridylacetoacetate (II). A 0.46-g (0.2 g-atom) sample of sodium was added in portions to a solution of 32.5 g (0.25 mole) of acetoacetic ester in 150 ml of dioxane, after which a solution of 25 g (0.1 mole) of pentachloropyridine in 100 ml of dioxane was added, and the mixture was refluxed with stirring for 5 h. The dioxane was removed by vacuum distillation, and the residue was treated with water acidified with HCl and extracted with ether. The ether solution was dried with Na_2SO_4, the ether was removed by distillation, and the residue was vacuum distilled to give 18.1 g (55%) of ester II at 111-114°C (0.04 mm) and 5.2 g (15%) of ester I at 120-125°C (0.04 mm).

4-Acetonyl-2,3,5,6-tetrachloropyridine (III). A mixture of 3.45 g (0.01 mole) of ester I in 20 ml of 80% H_2SO_4 was heated at 160°C for 1 h, after which it was cooled and poured over ice.

2,3,5,6-Tetrachloroisonicotinic Acid (IV). A 3-g (0.02 mole) sample of potassium permanganate was added with stirring at 80°C in the course of 4 h to a mixture of 1.4 g (5 mmole) of III in 30 ml of glacial acetic acid and 8 ml of 25% H_2SO_4, after which the excess potassium permanganate was decomposed by the addition of 5 ml of methanol. The hot solution was filtered, and the filtrate was vacuum evaporated. The residue after acidification with hydrochloric acid. The yield of product with mp 220-222°C (from water (mp 224-225°C [7]) was 0.26 g (20%).

2-Ethoxy-4-methyl-3,5,6-trichloropyridine (V). A 1.4-g (0.005 mole) of III was added to a solution of 0.23 g (0.01 g-atom) of sodium in 25 ml of absolute ethanol, and the mixture was refluxed for 6 h. The alcohol was removed by vacuum distillation, and the residue was diluted with water and worked up to give 1.1 g (95%) of a product with mp 50-52°C (from aqueous ethanol) (mp 48-50°C [1]).

2-Hydroxy-4-methyl-3,5,6-trichloropyridine (VI). A) A solution of 2.4 g (0.01 mole) of V in 10 ml of 80% H_2SO_4 was heated at 150°C for 20 min, after which it was poured over ice.

B) A 2.5-g (0.01 mole) sample of VII was heated on an oil bath at 240°C. The yield was 1.9 g (90%).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C*	Found,%		Empirical formula	Calc.,%		PMR spectrum, δ, ppm (in CCl_4)	Yield, %
		Cl	N		Cl	N		
I	93—95	41,1	4,0	$C_{11}H_9Cl_4NO_3$	41,2	4,1	1,52 (t, CH_3 ethyl, 2.1 (s, CH_3 acetyl), 4,52 (q, CH_2 ethyl, 13,4 (s, H enol)	60
II	76—77 bp 111—114 (0,04 mm)	41,0	4,0	$C_{11}H_9Cl_4NO_3$	41,2	4,1	1,52 (t, CH_3 ethyl, 2.2 (s, CH_3 acetyl), 4,52 (q, CH_2 ethyl), 13,3 (s, H enol)	55
III	101—103	51,8	5,0	$C_8H_5Cl_4NO$	52,0	5,1	—	86
VI	214—215	49,8	6,7	$C_6H_4Cl_3NO$	50,1	6,6	—	90
VII	227—228	41,8	5,6	$C_7H_4Cl_3NO_3$	41,5	5,4	—	80
VIIIa	58—60	38,3	3,6	$C_{13}H_{13}Cl_4NO_3$	38,1	3,7	—	78
VIIIb	bp 122—123 (0,03 mm)	34,6	3,6	$C_{16}H_{19}Cl_4NO_3$	34,2	3,4	—	75
IX	160—163 (dec.)	51,7	5,0	$C_7H_3Cl_4NO_2$	51,6	5,1	—	90
X	61—62	47,3	4,5	$C_9H_7Cl_4NO_2$	46,9	4,6	1,6 (t, CH_3 ethyl), 4,2 (s, CH_2 methylene), 4,47 (q, CH_2 ethyl)	70
XI	92—93	61,3	6,2	$C_6H_3Cl_4N$	61,4	6,1	—	95

* Compound VII was crystallized from water, and the remaining compounds were crystallized from aqueous ethanol.

2-Hydroxy-3,5,6-trichloro-4-pyridylacetic acid (VII). A 3.4 g (0.01 mole) sample of ester I was refluxed for 4 h in 50 ml of 25% KOH, after which the mixture was cooled, diluted with water, and acidified with HCl.

n-Butyl 2,3,5,6-Tetrachloro-4-pyridylacetoacetate (VIIIa). Concentrated HCl (25 ml) was added to a solution of 1.7 g (0.005 mole) of ester I in 25 ml of n-butyl alcohol, and the mixture was refluxed for 10 h. The alcohol was removed by vacuum distillation, and the residue was diluted with water.

n-Heptyl 2,3,5,6-Tetrachloro-4-pyridylacetoacetate (VIIIb). This compound was similarly obtained from ester I and n-heptyl alcohol.

3,4,5,6-Tetrachloro-2-pyridylacetic Acid (IX). A) A 3.4-g (0.01 mole) sample of ester II was heated in 20 ml of 80% H_2SO_4 at 115°C for 2 h, after which the mixture was poured over ice.

B) A mixture of 3.4 g (0.01 mole) of ester II in 100 ml of 2% NaOH was maintained at 20°C for 48 h, after which it was acidified with concentrated HCl and worked up to give 2.7 g (100%) of a product with mp 160-162°C.

C) A 3-g (0.01 mole) sample of ester X was heated in 20 ml of 80% H_2SO_4 at 115°C for 2 h, after which it was poured over ice and worked up to give 2.3 g (85%) of a product with mp 161-162°C.

Ethyl 3,4,5,6-Tetrachloro-2-pyridylacetate (X). A mixture of 3.4 g (0.01 mole) of ester II in 20 ml of 80% H_2SO_4 was maintained at 20°C for 24 h, after which it was diluted with water. The resulting oil crystallized completely on cooling.

2-Methyl-3,4,5,6-tetrachloropyridine (XI). A 2.7-g (0.01 mole) sample of acid IX was heated at 170°C for 1 h.

3,4,5,6-Tetrachloropicolinic Acid (XII). A 4.8-g sample of H_2SO_4 (sp. gr. 1.84) and 5 ml of water was added to a solution of 1.1 g (0.005 mole) of XI in 30 ml of acetic acid, and a solution of 7.2 g of potassium permanganate in 60 ml of acetic acid was added dropwise with stirring at 85° in the course of 3 h. Acid XII was isolated by the procedure used to isolate IV. The yield of product with mp 170-172°C (from aqueous ethanol) (mp 171-172°C [2]) was 0.5 g (38%).

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SYNTHESIS OF 6-NITRO-8-CHLORO-2,3-DIHYDRO-4(1H)-QUINOLONE

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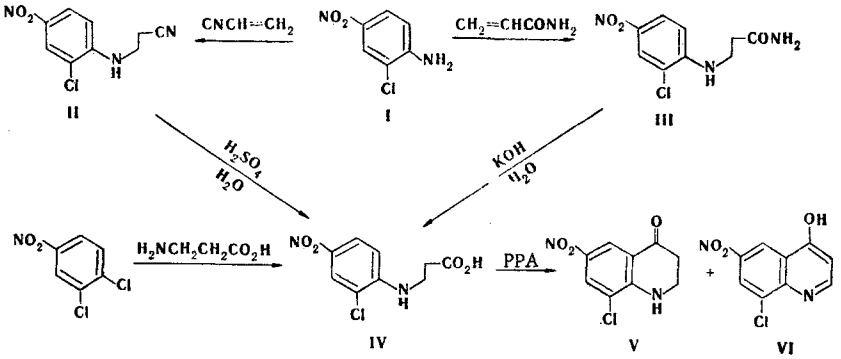
6-Nitro-8-chloro-2,3-dihydro-4(1H)-quinolone and its dehydrogenation product – 6-nitro-8-chloro-4-hydroxyquinoline – were isolated in the cyclization of N-(2-chloro-4-nitrophenyl-β-alanine in polyphosphoric acid.

In a continuation of our search for antiparasitic preparations in the dihydro-4-quinolone series [1, 2] we have synthesized the previously unknown 6-nitro-8-chloro-2,3-dihydro-4(1H)-quinolone (V) via the following scheme:



Cyanoethylation and carbamoylethylation of 2-chloro-4-nitroaniline (I) gave the nitrile (II) and amide (III) of N-(2-chloro-4-nitrophenyl)-β-alanine, which were saponified to N-(2-chloro-4-nitrophenyl)-β-alanine (IV). The latter was also obtained by reaction of 3,4-dichloronitrobenzene with β-alanine. The cyclization of alanine IV in polyphosphoric acid (PPa) gives, in addition to 2,3-dihydro-4-quinolone (V), 4-hydroxy-6-nitro-8-chloroquinoline (VI), the amount of which increases when heating is prolonged. Similar aromatization was also observed in the case of the cyclization of N-(o-nitrophenyl)-β-alanine [3], which led to the formation of 8-nitro-2,3-dihydro-4(1H)-quinolone and 8-chloro-4-quinolone. This process involves reduction of the nitro group, since the presence of a primary amino group was established in crude V by a qualitative test (diazotization and coupling with β-naphthol). This is confirmed by the formation of aminoquinolines in the dehydrogenation of tetrahydroquinolines [4].

Bands at 1673 (C=O), 3328 (NH), and 1330 cm^{-1} (NO_2) are observed in the IR spectrum of solid quinolone V. The band at 1350 cm^{-1} (NO_2) is retained in the spectrum of hydroxyquinoline VI, and a broad intense band at 3450 cm^{-1}, which should be assigned to the OH group, appears. This shows that the tautomeric equilibrium for VI in the crystalline state is shifted to favor the enol form. Compound VI evidently has a ketone form in solutions, including solutions in acetic acid, since V and VI form 2,4-dinitrophenylhydrazones. The UV spectra of alcohol solutions of quinolones V and VI contain three maxima that are close to the maxima of their chlorine-free analogs [5].

The PMR spectrum of V contains signals of methylene groups, and signals of protons attached to a conjugated double bond are observed in the spectrum of VI.

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