

JOHN BRAMMER PETERSEN, JØRGEN LEI,
NIELS CLAUSON-KAAS AND KJELD NORRIS

THE CHEMISTRY OF ENDIALONE

Det Kongelige Danske Videnskabernes Selskab
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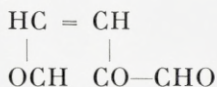
Kommissionær: Munksgaard
København 1967

Synopsis

29 pyridine compounds, 26 of which are new, have been prepared by oxidation of furfural with one or two moles of chlorine in water followed by reaction with amino compounds.

I. Introduction

cis-Oxoglutaconaldehyde (I) has never been prepared pure. But all existing knowledge indicates⁽¹⁾ that a solution of hydrates of I is formed in a high-yield reaction, when furfural is oxidized with chlorine or bromine in aqueous, acidic solution under certain reaction conditions.



I

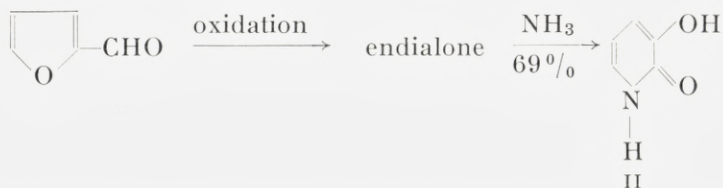
Such solutions are reasonably stable and have here been used to prepare a number of new compounds. The reactions leading to these compounds are in part general. Representative examples of the reactions are reported in this communication.

Solutions of *cis*-oxoglutaconaldehyde, as obtained by oxidation of furfural in water, are colourless. This means that molecules which contain two or more free carbonyl groups in conjugation cannot be present. No other information as to the structure of *cis*-oxoglutaconaldehyde in an aqueous solution is available. We believe such solutions contain a number of different molecular species, the concentrations of which depend upon the reaction conditions during their formation, as well as upon temperature, pH, concentration, and storage conditions of the solutions. Examples of the influence of age of a certain solution upon the yields of two different reactions, both with sulfamic acid, are given in the experimental part.

cis-Oxoglutaconaldehyde is, together with the corresponding *trans*-derivative, the simplest possible straight-chain compound having one double bond, two aldehyde groups, and one keto group. We use the trivial name endialone for the compound in whatever form it may exist in aqueous solution.

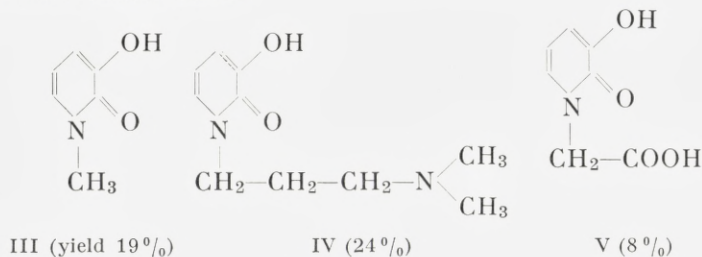
II. Endialone and Amino Compounds

(a) *Endialone and ammonia* give the known 3-hydroxy-2(1*H*)-pyridone (2,3-pyridinediol) (II). The experimental part of this paper contains a recipe according to which II is precipitated pure directly from the reaction mixture in a 45 per cent yield. Another, less convenient procedure describing isolation of II in a 69 per cent yield through prolonged continuous extraction of the reaction mixture with ether is also given.



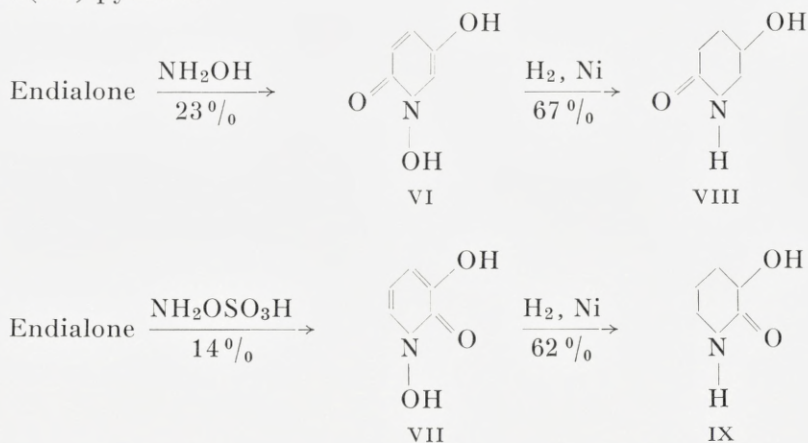
No detailed picture of the reaction leading to II can be given, since the exact structures of reactants and intermediates are unknown. The overall reaction consists of a connection of the two aldehyde groups of endialone through one ammonia molecule, followed by aromatization.

(b) *Endialone and primary aliphatic amines* similarly give 1-substituted 3-hydroxy-2(1*H*)-pyridones. Compounds III–V were prepared in this way. Attempts to prepare 1-substituted phenyl compounds from endialone and anilines were unsuccessful.

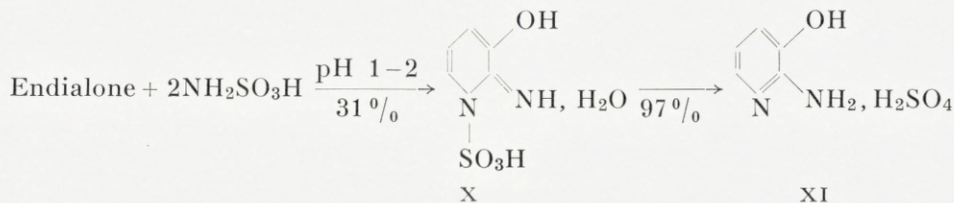


III is a known compound. It gives, as does the parent 3-hydroxy-2(1*H*)-pyridone, a strong and characteristic blue colour with ferric chloride. In Part III thirteen other 3-hydroxy-2(1*H*)-pyridones, all of which give similar blue ferric chloride reactions, are described. We therefore believe this reaction to be characteristic of the 3-hydroxy-2(1*H*)-pyridone structure (*cf.* Ref. 2). Since IV and V, which are new, also give the same blue ferric chloride reactions, we regard this as proof of the structures proposed for these two compounds.

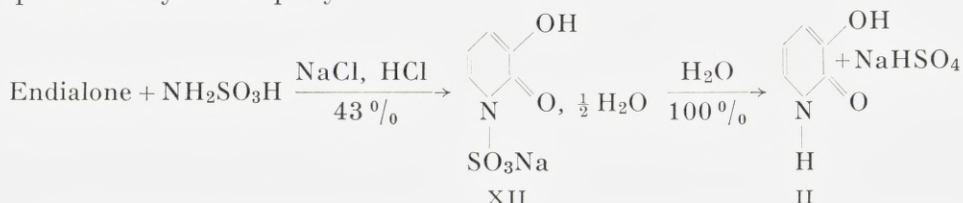
(c) *Endialone and hydroxylamine* give, by reaction at pH 2, the known 1,5-dihydroxy-2(1*H*)-pyridone (VI). With hydroxylamine-*O*-sulfonic acid in strongly acidic solution the new 1,3-dihydroxy-2(1*H*)-pyridone (VII) is formed. Both compounds were identified by catalytic hydrogenation to the corresponding hydroxypiperidones (VIII, respectively IX), which are known. VI is the only compound so far prepared from endialone and amino compounds, which is a 5-hydroxy-2(1*H*)-pyridone and not a 3-hydroxy-2(1*H*)-pyridone.



(d) *Endialone and sulfamic acid* give a mixture of two crystalline compounds, which in part precipitate from the reaction mixture. One of these compounds is predominantly formed in a rather slow reaction at pH 1–2, and may under these conditions be isolated pure from the reaction mixture by filtration and washing of the filter cake. The monohydrate structure X is proposed for this compound. It is slightly soluble in water, but forms a soluble sodium salt, which may be isolated pure as a semihydrate on evaporation of its solution. The sodium salt of X is stable, but the parent compound is, on standing, transformed slowly, on heating, rapidly, into 2-amino-3-pyridinol sulfate (XI) in a quantitative reaction.

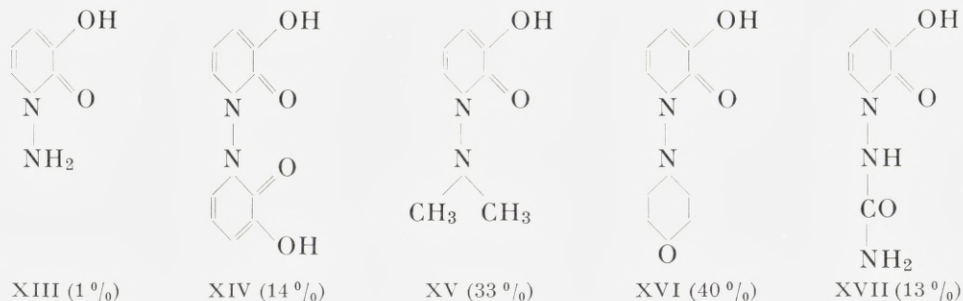


The second compound, which precipitates from mixtures of endialone and sulfamic acid containing sodium ions, is predominantly formed in a rapid reaction in a strongly acidic solution, and may under these conditions precipitate pure from the reaction mixture. The semihydrate structure XII is proposed for this compound. It is rather soluble in water and is stable in an alkaline solution. On standing, it is in part slowly transformed into 3-hydroxy-2(1*H*)-pyridone (II), on heating in an acidic aqueous solution, quantitatively and rapidly.



Both compounds prepared from endialone and sulfamic acid are new. The structures given (X and XII) are only to be regarded as proposals accounting for their formation, and for their transformation into 2-amino-3-pyridinol and 3-hydroxy-2(1*H*)-pyridone, respectively.

(e) *Endialone and hydrazino compounds* give the corresponding N-substituted 1-amino-3-hydroxy-2(1*H*)-pyridones, five of which



(XIII–XVII) have been prepared. Of these Compound XVII can, as expected, be hydrolyzed to XIII (yield 75%).

All five hydrazino compounds are new. They give a blue ferric chloride reaction proving the proposed structures. An acetate (XVIII) and a benzoate (XIX) of XV were prepared by conventional methods. Both are new and, as expected, give no ferric chloride reaction.

III. Endialone and Chlorine

When a strongly acidic solution of endialone is treated with chlorine, one mole is added to the double bond and a stable solution of hydrated 2,3-dichloro-4-oxoglutaraldehyde (XX) is formed. Proof of this is obtained by reaction of the solution with a number of amino compounds. Representative examples of such reactions, which are in part general, are given below.

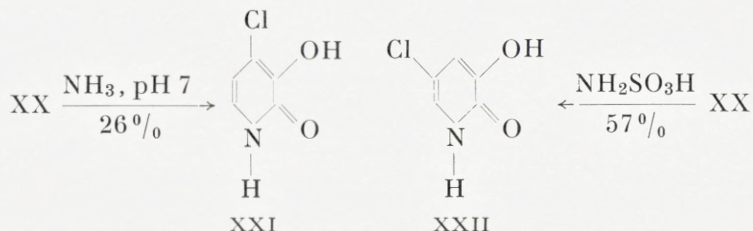


XX

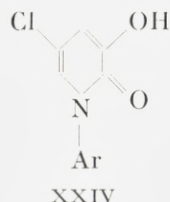
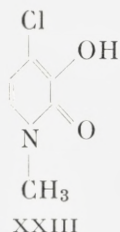
Solutions of hydrated 2,3-dichloro-4-oxoglutaraldehyde are colourless. This means that molecules which contain two free neighbouring carbonyl groups cannot be present. No other information as to the structure of XX in aqueous solution is available.

XX, like endialone, gives 2(1*H*)-pyridones by reactions with amino compounds. Altogether sixteen compounds, all of which are new, have been prepared. Again the overall reaction in each case consists of a connection of the two aldehyde groups through an amino group, followed by aromatization. All reaction products contain one chlorine atom, which must be situated in a β - or in γ -position. The positions of the chlorine atom as well as of the oxygen functions were in each case chosen on the basis of the NMR spectrum.

XX and ammonia give 4-chloro-3-hydroxy-2(1*H*)-pyridone (XXI) by reaction at pH 7. XX and sulfamic acid give the isomeric 5-chloro-3-hydroxy-2(1*H*)-pyridone (XXII) by reaction in strongly acidic solution. Both compounds give a blue ferric chloride reaction.

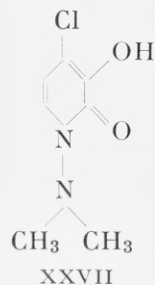
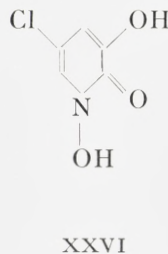
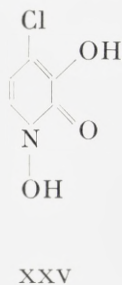


XX and methylamine give 4-chloro-3-hydroxy-1-methyl-2(1*H*)-pyridone (XXIII) (yield 21%) by reaction at pH 7.5. The compound gives a blue ferric chloride reaction.



Similarly XX and anilines give 1-aryl-5-chloro-3-hydroxy-2(1*H*)-pyridones (XXIV) by reaction in strongly acidic solution. Ten such compounds have been prepared in yields varying from 6 to 36 per cent. They all give a blue ferric chloride reaction.

XX and hydroxylamine give 4-chloro-1,3-dihydroxy-2(1*H*)-pyridone (XXV) (yield 15%) by reaction at pH 4. The same reactants in a more acidic solution give the isomeric 5-chloro-1,3-dihydroxy-2(1*H*)-pyridone (XXVI) (yield 17%).



XX and *N,N*-dimethylhydrazine give 4-chloro-1-dimethylamino-3-hydroxy-2(1*H*)-pyridone (XXVII) by reaction in acidic solution. The compound gives a blue ferric chloride reaction.

It will be noted that all compounds mentioned in this part are 3-hydroxy-2(1*H*)-pyridones. Furthermore, that reactions carried out in neutral or slightly acidic solution give γ -chloro compounds, while, with one exception (XXVII), reactions carried out in more acidic solutions give β -chloro compounds.

IV. Discussion of Results

The new syntheses of pyridine compounds described here are as a rule sensitive to slight changes of the reaction conditions, and low-yield syntheses always give a corresponding large amount of dark resinous or solid polymeric

material. This behaviour, which is typical of reactions with furan compounds, is understandable, considering the structures of the compounds involved and the complexity of the reactions. Each preparation consequently requires much experimental work in order to find reaction conditions which give a good yield. If, however, such conditions have first been found for any particular compound, then the actual preparation is both cheap and simple, since in each case, from a preparative point of view, it is a one-step reaction from furfural.

As mentioned in the introduction, most of the syntheses are representative examples of general reactions. They exemplify and extend the principle of using furans as a source for the production of 1,4-dicarbonyl compounds as recommended in a former publication in these communications⁽³⁾.

V. Summary

29 pyridine compounds, 26 of which are new, have been prepared by oxidation of furfural with one or two moles of chlorine in water followed by reaction with amino compounds.

VI. Experimental

Preparation of a molar solution of endialone. Chlorine (70.9 g, 1.00 mole) is passed into a well-stirred emulsion of furfural (96.1 g, 1.00 mole) in water (700 ml) at 0° over a period of 30 min. Furfural dissolves during the reaction. At the same time a minor amount of an oily precipitate, which sticks to the wall of the reaction vessel, is formed. 40% Sodium hydroxide solution (about 200 g, 2.00 mole) is added dropwise with stirring, until pH of the solution is 2.0. The mixture is decanted from the oily precipitate and diluted with water to 1000 ml and stored at -25°.

The almost colourless solution, assuming that a quantitative reaction has taken place, is molar with respect to endialone and two-molar with respect to sodium chloride. Where nothing else is stated, the solution has been used in the following preparations and been described as being molar with respect to endialone.

Preparation of 3-hydroxy-2(1H)-pyridone (II) (yield 45%). Furfural (139 g, 1.45 mole), sodium bromide (20 g), water (400 ml), t-butyl alcohol (200 ml), and concentrated hydrochloric acid (60 ml) are mixed in a two

litre reaction flask to give a clear solution. Sodium hypochlorite solution (about 700 ml, 1.45 mole of chlorine) is added dropwise with stirring and cooling at 0° over a period of 45 min. During addition the pH of the reaction mixture rises due to sodium hydroxide present in the hypochlorite solution. If the value 1.0 should be reached, then 40 ml of concentrated hydrochloric acid is added in one portion. A few minutes after the addition of hypochlorite solution is completed, powdered ammonium chloride (200 g) is added in one portion, and the pH immediately afterwards brought as rapidly as possible to 7.5 by the addition of concentrated ammonium hydroxide solution, and automatically kept there for 20 min. by the further addition of concentrated ammonium hydroxide solution (use a thin-walled, rapidly indicating glass electrode). During this time the temperature of the reaction mixture is regulated by external cooling in such a way that it rises to $6-8^{\circ}$ in 2-4 min. (precipitation of II begins), remains there for another 2-4 min., and finally drops to 5° , and remains there for the rest of the time. After this period of 20 min. the pH of the reaction mixture is brought to 5 by the addition of concentrated hydrochloric acid, and the mixture then cooled to 0° in 5 min. The precipitate of yellowish brown crystals is isolated by rapid filtration, washed with water (700 ml), t-butyl alcohol (100 ml), and ether (250 ml), and dried at 120° . 70-75 g (about 45%) of II is in this way obtained as a light brown powder, m.p. $251-253^{\circ}$ (in an evacuated tube, corr.).

Preparation of 3-hydroxy-2(1H)-pyridone (II) (yield 69%). Furfural (9.61 g, 0.100 mole) was dissolved in N hydrochloric acid (150 ml). Sodium hypochlorite solution (about 56 ml, 0.105 mole of chlorine) was added dropwise with stirring and cooling at 0° over a period of 15 min. The resulting solution of endialone was then added dropwise with stirring over a period of 1 hour to an emulsion of ether (50 ml) and aqueous ammonium chloride (25 g in 70 ml) at 20° . During the addition the pH of the reaction mixture was automatically kept at 7.5 by the addition of concentrated ammonium hydroxide solution. After the reaction the mixture was continuously extracted with ether, whereby 7.8 g of crude II was isolated as a brown powder. Sublimation gave 7.67 g (69%) of an almost white product, m.p. $246-254^{\circ}$.

3-Hydroxy-1-methyl-2(1H)-pyridone (III). A solution containing 0.10 mole of endialone was prepared from furfural and sodium hypochlorite solution as described in the preceding experiment. A 33% aqueous solution of methylamine (14.1 g, 0.15 mole) was added during 1 min. with stirring, whereby the temperature of the reaction mixture rose from 0° to about 15° . The pH of the solution was brought to 7.5 and kept there for 30 min. by the

addition of 40% sodium hydroxide solution (4.9 ml in all). During this time the temperature was kept at 15°. The very dark reaction mixture was then heated to 75°, cooled to room temperature, brought to pH 4 by the addition of concentrated hydrochloric acid (about 2 ml), and continuously extracted with ether overnight. 2.90 g of material, m.p. 123–127°, was isolated in this way. Sublimation (115°, 0.1 mm) followed by crystallization from carbon tetrachloride (35 ml) gave 2.38 g (19%) of white crystals of III, m.p. 130–132°; previously found 131°⁽⁴⁾. [Found: C 57.3; H 5.7; N 10.9. Calc. for C₆H₇NO₂ (125.1); C 57.6; H 5.6; N 11.2]. The product gave a strong blue ferric chloride reaction.

1-[3-(Dimethylamino)propyl]-3-hydroxy-2(1H)-pyridone (IV). A solution containing 0.100 mole of endialone was prepared as in the preceding experiment. 3N hydrochloric acid (17 ml) and then N,N-dimethyl-1,3-propanediamine (10.2 g, 0.100 mole) were added, both in one portion, whereby the temperature of the reaction mixture rose from 0° to about 20°. After a few minutes the red mixture was cooled to 10°. The pH of the solution was brought to and kept at 7.5 for 15 min. by the addition of 40% sodium hydroxide solution (6.2 ml in all). During this time the temperature rose to 20°. The very dark reaction mixture was heated to 70°, kept there for 10 min., cooled to room temperature and brought to pH 9 by the addition of 40% sodium hydroxide solution (about 3 ml). Continuous extraction with ether (48 hours) and distillation of the ethereal extract gave 5.65 g of an oil, b_{0.2} 112–117°, which rapidly turned yellowish red on exposure to air. The oil was dissolved in 99% ethanol (40 ml). A solution of 85% phosphoric acid (3.34 g) in ethanol (10 ml) was added dropwise with stirring over 5 min., whereby a white precipitate was formed. The mixture was heated under reflux (15 min.), cooled and filtered. The filter cake was washed with ethanol and dried. 7.01 g (24%) of almost white crystals of the phosphate of IV m.p. 210–212° was obtained in this way. [Found: C 40.8; H 6.8; N 9.5; P 10.4. Calc. for C₁₀H₁₉N₂O₆P (294.3): C 40.8; H 6.5; N 9.5; P 10.5]. Another crystallization from 80%-ethanol gave 6.28 g of material melting at 213–214°. Further crystallization did not change the melting point. The product gave a strong blue ferric chloride reaction.

3-Hydroxy-2-oxo-1(2H)-pyridineacetic acid (V). This compound was prepared from furfural (0.100 mole), sodium hypochlorite solution (0.105 mole), and glycine (7.50 g, 0.100 mole), as described in the pre-

paration of III. The final reaction mixture (pH 7.5) was acidified with concentrated hydrochloric acid (15 ml) and continuously extracted with ether (48 hours). The ethereal extract (about 75 ml) was a suspension of crystals, which were filtered off (4.3 g) and recrystallized from dioxane (45 ml). 2.4 g of crystals, m.p. 213–216° was obtained in this way. Two further crystallizations gave 1.32 g (8%) of V, m.p. 217–219°. [Found: C 49.6; H 4.3; N 8.4. Calc. for $C_7H_7NO_4$ (169.1): C 49.7; H 4.2; N 8.3]. The product gave a strong blue ferric chloride reaction.

A sodium salt monohydrate was prepared in the usual way, m.p. 280–283° (dec.). Water is given off at about 180°. [Found: C 40.2; H 4.0; N 6.6. Calc. for $C_7H_8NNaO_5$ (209.1): C 40.2; H 3.9; N 6.7].

1,5-Dihydroxy-2(1H)-pyridone (VI). Hydroxylamine hydrochloride (7.0 g, 0.100 mole) was dissolved in a stirred solution of freshly prepared endialone (100 ml, 0.100 mole) at 0°. 40% Sodium hydroxide solution was automatically added to the clear solution at 0°, pH being kept at 2.0. Crystals began to separate after 5–10 min. After 1 hour practically no more sodium hydroxide was consumed by the reaction. In all 6.5 ml (0.093 mole) had been added at this time. The precipitate was filtered off, washed with water, and crystallized from water (330 ml) with carbon black. The crystals were filtered off, washed with water, and dried (0.1 mm, 20°, overnight). 2.88 g (23%) of VI was obtained in this way. [Found: C 47.2; H 4.0; N 10.9. Calc. for $C_5H_5NO_3$ (127.1): C 47.3; H 4.0; N 11.0]. The product, as described previously⁽⁵⁾, melted partially with destruction around 220° (in an evacuated tube), and gave a strong violet ferric chloride reaction.

1,3-Dihydroxy-2(1H)-pyridone (VII). 90% Hydroxylamine-O-sulfonic acid⁽⁶⁾ (12.5 g, 0.10 mole) was dissolved in a stirred solution of freshly prepared endialone (100 ml, 0.100 mole) at 0°. After 7 min. concentrated hydrochloric acid (50 ml) of room temperature was added in one portion with cooling. The temperature rose immediately to 15°. The mixture was now kept at 15° for 2 hours, during which time the solution became dark red, but remained practically clear. Neutralization at 20° to pH 3.5 with 40% sodium hydroxide solution (about 60 ml), continuous extraction with ether for 2 days, and evaporation of the ethereal suspension to dryness gave a very dark semi-solid residue, which after washing with two 5 ml portions of methanol gave 2.05 g of impure VII. Sublimation (150°, 0.5 mm) gave 1.96 g of slightly yellow crystals, m.p. 183–187°. Crystallization from n-butanol finally gave 1.74 g of pure VII (14%), m.p. 188–190°. Further

crystallization did not change the melting point. [Found: C 47.4; H 4.0; N 11.1. Calc. for $C_5H_5NO_3$ (127.1): C 47.3; H 4.0; N 11.0]. The product gave a strong red ferric chloride reaction.

5-Hydroxy-2-piperidone (VIII). 0.64 g of VI was hydrogenated as described in the literature⁽⁵⁾. The yield of crystallized VIII was 0.39 g (67%), m.p. 144–146°. [Found: C 52.1; H 7.9; N 12.0. Calc. for $C_5H_9NO_2$ (115.1): C 52.2; H 7.9; N 12.2]. The identity with the product described in the literature⁽⁵⁾ was established spectroscopically (IR in KBr).

3-Hydroxy-2-piperidone (IX). 0.64 g of VII was hydrogenated as described for the hydrogenation of 3-hydroxy-2(1*H*)-pyridone⁽⁷⁾. The reaction product was sublimated (100–110°, 0.1 mm), yielding 0.36 g of IX (62%) as white crystals, melting point and mixed melting point with an authentic sample 133–135°, mixed melting point with VIII 107–115°. [Found: C 52.4; H 7.9; N 11.9. Calc. for $C_5H_9NO_2$ (115.1): C 52.2; H 7.9; N 12.2]. The product was furthermore identified spectroscopically (IR in KBr).

Reaction of endialone and sulfamic acid at pH 1–2. A solution of sodium sulfamate is prepared by dissolving sulfamic acid (194 g, 2.00 mole) in water (500 ml) and 40% sodium hydroxide solution (200 g). A solution of freshly prepared endialone (1000 ml, 1.00 mole) is added in one portion at 10°. pH of the solution is adjusted to 1.7 by the addition of 3 N hydrochloric acid (about 50 ml) and the resulting clear, slightly yellow solution left standing at 10° with stirring. After about 15 min. X begins to precipitate as an almost white powder. After 3 hours the precipitate is isolated by filtration, washed with water (300 ml), methanol (200 ml), and ether, and dried (20°, 1 mm, 2 hours). The yield of almost white crystals of X is 64.5 g (31%). [Found: C 29.0; H 4.0; N 12.9; S 15.5; H₂O (Karl Fischer) 8.2. Calc. for $C_5H_6N_2O_4S \cdot H_2O$ (208.2): C 28.8; H 3.9; N 13.4; S 15.4; H₂O 8.7]. Repetition of the experiment gave 66.6 g (32%) of X.

Addition of concentrated hydrochloric acid (40 ml) to the mother liquid from X, heating under reflux for 5 min., addition of sodium hydroxide solution to pH 4.5, and continuous extraction with ether gave 10.0 g of 3-hydroxy-2(1*H*)-pyridone (9%).

*Properties of 3-hydroxy-2-imino-1(2*H*)-pyridinesulfonic acid hydrate (X)*. X is practically insoluble in cold water and in organic solvents. It melts at 70–90°, dependent on the rate of heating. At 10–20° above the melting point

it crystallizes (formation of 2-amino-3-pyridinol sulfate), to melt again at 124–125°. It gives a blue ferric chloride reaction.

X (1.0 g) was crystallized very rapidly from water (50 ml) in an 85% yield. The crystallized product was white and gave only one spot when investigated by thin layer chromatography (on "Kieselgel G" in methanol). After standing for four days at room temperature, it was apparent from the chromatogram that the product had been partly transformed into 2-amino-3-pyridinol and sulfuric acid.

A preparative, almost quantitative transformation of X (64.5 g) into 2-amino-3-pyridinol was carried out by heating with water (200 ml) under reflux (5 min.), cooling to room temperature, adding 40% sodium hydroxide solution, until pH of the mixture was 8.0 (about 65 g), and continuously extracting the resulting suspension of crystals with ether. 32.8 g (97%) of 2-amino-3-pyridinol was obtained in this way. The product melted in an evacuated tube at 172–174° (polymorphic changes of the crystals appear to take place at temperatures near the melting point).

3-Hydroxy-2-imino-1(2H)-pyridinesulfonic acid sodium salt semihydrate. Freshly prepared X (3.40 g, 0.0163 mole), 98% sodium hydroxide (0.665 g, 0.0163 mole), and water (10 ml) were mixed to give an almost clear, slightly yellow solution, which was evaporated to dryness under 15 mm from a water bath (100°). 3.43 g of a greyish-white powder was scratched out of the flask. [Found: C 27.3; H 2.8; N 12.6; S 14.5; H₂O (Karl Fischer) 3.7. Calc. for C₅H₅N₂NaO₄S, $\frac{1}{2}$ H₂O (221.2): C 27.2; H 2.7; N 12.7; S 14.4; H₂O 4.1].

The product was stable to heating under reflux for 20 min. in N sodium hydroxide solution. It formed no precipitate with barium chloride.

Reaction of endialone and sulfamic acid in 3 N acid solution. Powdered sulfamic acid (30.0 g, 0.31 mole), water (100 ml), and concentrated hydrochloric acid (60 ml) are placed in a one litre reaction flask, and the suspension cooled to -5°. A four week old solution (stored at -25°) of endialone (200 ml, 0.200 mole) of -10° is added in one portion. The mixture is stirred efficiently at 10° for 1 hour. Precipitation of XII begins after 5 min., whereby the mixture is rapidly transformed into a thin paste. Ethanol (350 ml) is added, the suspension cooled with stirring to -10°, and filtered through a sintered glass disk. The cake of white crystals is washed on the filter (without stirring) with ethanol (80 ml) and ether. The crystals are dried in a thin layer on paper at room temperature. The yield of XII is 19.2 g (43%).

[Found: C 26.8; H 2.5; ashes in CH determination 32.1; N 6.2; S 14.1; H₂O (Karl Fischer) 4.6. Calc. for C₅H₄NNaO₅S, $\frac{1}{2}$ H₂O (222.2): C 27.0; H 2.3; ashes if Na₂SO₄ 31.9; N 6.3; S 14.4; H₂O 4.1].

Boiling of the mother liquor from XII for a few minutes, followed by cooling and addition of sodium hydroxide solution to pH 4.5, and continuous extraction with ether gave 2.2 g of 3-hydroxy-2(1*H*)-pyridone (10%).

Properties of 3-hydroxy-2-oxo-1(2H)-pyridinesulfonic acid sodium salt semihydrate (XII). XII shows no sharp melting point. It is rather soluble in water. The solution shows pH 5, gives a blue ferric chloride reaction, and no precipitate with barium chloride. After heating to 100° the solution is more acid (pH 1–2) and gives a precipitate with barium chloride (formation of 3-hydroxy-2(1*H*)-pyridone and sodium hydrogen sulfate).

If XII is dissolved in N sodium hydroxide and the solution heated to boiling, no precipitate of barium sulfate is formed after cooling, acidification, and addition of barium chloride.

A preparative, quantitative transformation of XII (15.0 g, 0.068 mole) into 3-hydroxy-2(1*H*)-pyridone was carried out by heating with water (75 ml) under reflux (15 min.), cooling to room temperature, adding 98% sodium hydroxide pellets (2.75 g, 0.068 mole), and continuously extracting the resulting suspension of crystals with ether. 7.56 g (100%) of 3-hydroxy-2(1*H*)-pyridone was obtained in this way, m.p. in an evacuated tube 253–254°.

Experiments on the change of endialone solutions with time. Apart from the experiments described above, compounds X and XII were also prepared from endialone solutions stored at –25° for various lengths of time. The yields of all preparations are summarized in Table 1.

1-Amino-3-hydroxy-2(1H)-pyridone (XIII) from endialone. To a freshly prepared solution of endialone (50 ml, 0.050 mole) of 0° concentrated hydrochloric acid (25 ml) was added in one portion with cooling and stirring.

TABLE 1. Experiments on the change of endialone solutions with time.

Age of endialone solution, days	Yield of X %	Yield of XII %
0	31, 32	37
4	28	
15	28	
28		43

The temperature was allowed to rise to 10° . Finely powdered hydrazine sulfate (6.5 g, 0.050 mole) was added and the mixture kept at 10° for 30 min., heated to 50° and kept there for another 30 min. The reaction mixture was cooled to 20° , brought to pH 4.5 with a 40% sodium hydroxide solution (cooling), and continuously extracted with ether overnight. Evaporation of the ether and washing of the semi-solid residue with a small amount of methanol gave a crystalline product, which was purified by sublimation (130° , 0.2 mm) to give 90 mg of white crystals, m.p. $150-158^{\circ}$. Crystallization from methanol gave 45 mg (1%) of XIII, m.p. $161-163^{\circ}$. The product, which gave a strong blue ferric chloride reaction, was identified by means of its infrared spectrum (in KBr, see below).

3,3'-Dihydroxy-2,2'-dioxo-1(2H),1'(2'H)-bipyridine (XIV). To a freshly prepared solution of endialone (100 ml, 0.100 mole) of 0° concentrated hydrochloric acid (50 ml) was added in one portion with cooling and stirring. The temperature was allowed to rise to 10° . Finely powdered hydrazine sulfate (5.2 g, 0.040 mole) was added, and the mixture kept at 10° with stirring for 2 hours, during which time it turned brownish red. Precipitation of crude XIV began after a few minutes. The product was filtered off, washed with water and methanol, and dried (100° , 1 hour). The yield was 2.72 g (brown powder). Crystallization from water (500 ml) with carbon black gave 1.25 g (14%) of XIV as white needles, which decomposed above 300° . [Found: C 54.8; H 3.7; N 12.7. Calc. for $C_{10}H_8N_2O_4$ (220.2): C 54.6; H 3.7; N 12.7]. The product gave a strong blue ferric chloride reaction.

1-(Dimethylamino)-3-hydroxy-2(1H)-pyridone (XV). To a freshly prepared solution of endialone (200 ml, 0.200 mole) was added concentrated hydrochloric acid (20 ml), and then N,N-dimethylhydrazine (12.0 g, 0.20 mole) at 0° with cooling and stirring. The mixture was heated to 60° , and kept there for 1 hour. The colour of the mixture gradually changed from orange through deep red to dark brown. The mixture was cooled to 20° , neutralized with a 40% sodium hydroxide solution (about 20 ml), and continuously extracted with ether overnight. After removal of the ether the resulting residue was distilled. The fraction boiling at $113-123^{\circ}$ under 15 mm (12.2 g) was collected, dissolved in boiling cyclohexane (30 ml), and the solution cooled to 10° with shaking. The resulting crystals were filtered off and washed with 5 + 10 ml of cyclohexane. 10.2 g (33%) of white crystals of XV were obtained in this way, m.p. $81-83^{\circ}$. [Found: C 54.7; H 6.7; N 18.1. Calc. for $C_7H_{10}N_2O_2$ (154.2): C 54.5; H 6.5; N 18.2]. The product gave a strong blue ferric chloride reaction.

4-[3-Hydroxy-2-oxo-1(2H)-pyridyl]morpholine (XVI). A solution of pH 1 of 4-aminomorpholine (5.1 g, 0.050 mole) in hydrochloric acid (volume about 100 ml) was added to a freshly prepared solution of endialone (50 ml, 0.050 mole). The mixture was heated to 60°, while the pH was automatically kept at 1.0 by the addition of 40% sodium hydroxide solution. The mixture, which darkened more and more, was kept at pH 1.0 and 60° for 30 min., cooled to room temperature, adjusted to pH 3.5, and continuously extracted with ether overnight. Evaporation of the ether gave 5.73 g of brown material, which after sublimation (150°, 0.1 mm) gave 4.49 g (46%) of slightly yellow crystals of XVI, m.p. 174–177°. Crystallization from toluene (25 ml) gave 3.92 g (40%) of white crystals, m.p. 177–179°. Further crystallization did not change the melting point. [Found: C 55.1; H 6.1; N 14.1. Calc. for C₉H₁₂N₂O₃ (196.2): C 55.1; H 6.2; N 14.3]. The product gave a strong blue ferric chloride reaction.

1-[3-Hydroxy-2-oxo-1(2H)-pyridyl]urea (XVII) was prepared from equimolar amounts of endialone and semicarbazide hydrochloride by reaction at 10–50°. The best yield of analytically pure material obtained in one among 22 experiments was 13%, but no reproducible directions for the synthesis have been found so far; white crystals from water, m.p. 233–235° (decomp.). [Found: C 42.7; H 4.3; N 24.9. Calc. for C₆H₇N₃O₃ (169.1): C 42.6; H 4.2; N 24.9]. The product gave a strong blue ferric chloride reaction.

1-Amino-3-hydroxy-2(1H)-pyridone (XIII) from XVII. XVII (1.34 g) was dissolved and heated under reflux (80 min.) in 6 N hydrochloric acid (100 ml). The reaction mixture was cooled to room temperature, brought to pH 5.0 by the addition of a 40% sodium hydroxide solution (about 42 ml), and continuously extracted with ether overnight. 0.75 g (75%) of XIII, m.p. 161–163°, was obtained in this way. [Found: C 47.7; H 4.7; N 22.2. Calc. for C₅H₆N₂O₂ (126.1): C 47.6; H 4.8; N 22.2]. The IR spectrum in KBr was identical with that of the sample of XIII prepared from endialone and hydrazine.

1-(Dimethylamino)-3-hydroxy-2(1H)-pyridone acetate (XVIII). XV (1.00 g) was dissolved in a mixture of acetic anhydride (5 ml) and pyridine (5 ml), and the solution left at room temperature overnight. After removal of the solvent, the oily residue (1.25 g) was distilled, yielding 1.17 g (92%) of XVIII, b_{0,4} 102°, slightly yellow oil, n_D²⁵ 1.5232. The oil crystallized on

standing to white crystals melting at 48–49°. [Found: C 55.3; H 6.1; N 14.2. Calc. for $C_9H_{12}N_2O_3$ (196.2): C 55.1; H 6.2; N 14.3].

The product may be crystallized from ether-benzine (40–65°) at –20° (m.p. of crystallized product 49–50°). Its aqueous solution gave no ferric chloride reaction. The infrared spectrum in KBr showed absorption bands at 1665 cm^{-1} (amide-carbonyl) and at 1767 cm^{-1} (ester-carbonyl).

1-(Dimethylamino)-3-hydroxy-2(1H)-pyridone benzoate (XIX). XV (5.00 g, 0.0325 mole) was dissolved in pyridine (30 ml). Benzoyl chloride (7.05 g, 0.0500 mole) was added dropwise at room temperature with stirring. The mixture was left overnight, and then poured on ice-water (200 ml). The white precipitate formed was filtered off, washed with water, and dried (20°, 0.1 mm). 8.43 g of white crystals, m.p. 121–131°, were obtained in this way. Crystallization from cyclohexane (250 ml) gave 6.75 g (81%) of XIX, m.p. 137–138°. [Found: C 65.1; H 5.5; N 10.9. Calc. for $C_{14}H_{14}N_2O_3$ (258.3): C 65.1; H 5.5; N 10.9].

The product gave no ferric chloride reaction. The infrared spectrum in KBr showed absorption bands at 1660 cm^{-1} (amide-carbonyl) and at 1740 cm^{-1} (ester-carbonyl).

Preparation of a molar solution of 2,3-dichloro-4-oxoglutaraldehyde (XX). Chlorine (70.9 g, 1.00 mole) is passed through a cylindrical sintered glass tube into a vigorously stirred emulsion of freshly distilled furfural (48.0 g, 0.500 mole) in water (350 ml) over a period of 1 hour 40 min. at 0°. After half of the chlorine has been added (40 min.), concentrated hydrochloric acid (42 ml, 0.50 mole) and polypropyleneglycol (5 drops of No. 2025 from Union Carbide) are added, the latter to prevent foaming. After the addition of all chlorine the reaction mixture is stirred for 30 min. at –5° to 0°, filtered from a small amount of a sticky precipitate, diluted with water to 500 ml, and stored at –25°, at which temperature the solution is stable for at least six months.

Assuming that a quantitative reaction has taken place, the solution is molar with respect to XX, and 3 N with respect to hydrochloric acid. It has been used in the following preparations and been described as being molar with respect to XX.

4-Chloro-3-hydroxy-2(1H)-pyridone (XXI). Concentrated ammonium hydroxide solution (about 25 ml) was added rapidly to a solution of XX

(100 ml, 0.100 mole) at 0° (external cooling), until pH of the reaction mixture was 7.0. The reaction flask was removed from the cooling bath, and the pH kept at 7.0 by automatic addition of ammonium hydroxide solution. After about 5 min. a yellow precipitate was formed. During the reaction the temperature of the reaction mixture rose to around 35°, and the mixture turned very dark. When, after about 30 min., a total amount of about 42 ml of ammonium hydroxide had been added, the reaction was complete. The dark suspension was cooled to 15° and brought to pH 4.0 by the addition of concentrated hydrochloric acid (1–2 ml). After a few minutes the precipitate was filtered off, washed twice with water, and dried (80°, 15 hours). The yield was 10.0 g of a black powder.

2.00 g was crystallized from acetic acid (80 ml) with carbon black (0.5 g), giving 0.76 g (26% based upon furfural) of light grey plates of XXI, melting in an evacuated tube with darkening decomposition at 290–295°. Further crystallizations did not change the IR spectrum (in KBr). [Found: C 41.5; H 2.9; Cl 24.3; N 9.5. Calc. for C₅H₄ClNO₂ (145.6): C 41.3; H 2.8; Cl 24.4; N 9.6]. The product gave a strong blue ferric chloride reaction.

5-Chloro-3-hydroxy-2(1H)-pyridone (XXII). Sulfamic acid (75 g, 0.77 mole) was added to a solution of XX (500 ml, 0.500 mole), and the resulting slurry heated to 50° during 10 min. with stirring. The acid dissolved, and the reaction mixture turned orange red. After a few minutes at 50°, XXII began to separate as a light yellow precipitate. The mixture was kept at 50° for 1 hour, cooled to 10°, kept there for 15 min., and the precipitate filtered off and dried at 80° overnight. 48 g of a light brown powder was obtained in this way.

Sublimation (200°, 0.2 mm, 90 min.) of 250 mg gave 215 mg of XXII as white crystals, melting in an evacuated tube with darkening and decomposition at 290–295°. The amount corresponds to a yield of 57%, based upon furfural. The IR spectrum (in KBr) was radically different from that of 4-chloro-3-hydroxy-2(1H)-pyridone (XXI). [Found: C 41.5; H 2.9; Cl 24.3; N 9.4. Calc. for C₅H₄ClNO₂ (145.6): C 41.3; H 2.8; Cl 24.4; N 9.6]. The product gave a strong blue ferric chloride reaction.

Crystallization from acetic acid may be used to purify larger amounts of crude material. Thus 5.00 g gave 3.34 g of analytically pure XXII when crystallized from acetic acid (70 ml) with carbon black (1 g). The amount corresponds to a yield of 44%, based upon furfural.

An identical preparation made from a 6 months old solution of XX, stored at –25°, gave a 53% yield of XXII.

4-Chloro-3-hydroxy-1-methyl-2(1H)-pyridone (XXIII). A 33% aqueous solution of methylamine (21.0 ml, 0.20 mole) was added dropwise with stirring over a few minutes to a solution of XX (200 ml, 0.20 mole) of -20° . The temperature rose to -5° . pH of the faintly yellow mixture was brought to 7.5 by dropwise addition of 40% sodium hydroxide solution, and automatically kept at this value for 45 min. by further addition of sodium hydroxide solution. The reaction temperature was at the same time kept at 0° . The temperature of the dark brown reaction mixture was now raised to room temperature in an hour, pH still being kept at 7.5. The total amount of sodium hydroxide solution added was 34.5 ml. Concentrated hydrochloric acid (about 9 ml) was added dropwise until pH 3, and the mixture then continuously extracted with ether overnight. Evaporation of the ethereal extract, sublimation of the residue (150° , 0.5 mm), and two crystallizations from absolute ethanol gave 6.86 g (21%) of XXIII, m.p. $186-187^{\circ}$. [Found: C 45.1; H 3.9; Cl 22.2; N 8.9. Calc. for $C_6H_6ClNO_2$ (159.6): C 45.2; H 3.8; Cl 22.2; N 8.8]. The product gave a strong blue ferric chloride reaction.

1-Aryl-5-chloro-3-hydroxy-2(1H)-pyridones (XXIV). The appropriate aniline (0.1 mole) (solid anilines were crushed to a fine powder before use) was added to a solution of XX (100 ml, 0.1 mole) of -20° . The resulting solution or suspension (in some cases the hydrochlorides of the anilines may not be soluble in the reaction mixture at lower temperature) was heated with stirring to 90° and kept there for 30 min. During this time the reaction mixture turned dark, and a sticky black tar was usually formed. The reaction mixture was cooled to 55° , and extracted several times with chloroform at this temperature. The solvent was removed from the combined chloroform extracts by distillation, and the residue sublimated at $175-200^{\circ}$ under 0.5 mm. The sublimate was crystallized from 99% ethanol or from ethanol-water (1:1) to yield the pure 2(1H)-pyridones. These all gave a strong blue ferric chloride reaction. Data for the ten compounds prepared are given in Table 2.

4-Chloro-1,3-dihydroxy-2(1H)-pyridone (XXV). Hydroxylamine hydrochloride (34.8 g, 0.500 mole) was added in one portion to a solution of XX (500 ml, 0.500 mole) of -20° . The resulting solution was brought to pH 4.0 by dropwise addition of 40% sodium hydroxide solution. At the same time the temperature of the reaction mixture was allowed to rise to 0° . pH of the mixture was now automatically kept at 4.0 by further addition of sodium hydroxide solution, while the temperature was brought to 60° and kept

TABLE 2. 1-Aryl-5-chloro-3-hydroxy-2(1*H*)-pyridones.

Substituents in the phenyl group (Ar) of structure XXIV	Yield %	m. p., °C	Formula (M)	Analyses				
					C	H	Cl	N
None.....	21	147—149°	C ₁₁ H ₈ ClNO ₂ (221.6)	Found	59.5	3.7	16.1	6.3
				Calc.	59.7	3.6	16.0	6.3
2-Methyl.....	6	172—173°	C ₁₂ H ₁₀ ClNO ₂ (235.7)	Found	61.2	4.4	15.1	6.1
				Calc.	61.2	4.2	15.1	5.9
3-Methyl.....	16	158—160°	—	Found	61.4	4.4	15.0	6.0
4-Methoxy.....	14	172—174°	C ₁₂ H ₁₀ ClNO ₃ (251.7)	Found	57.4	4.2	14.0	5.6
				Calc.	57.3	4.0	14.1	5.6
2-Chloro.....	6	164—165°	C ₁₁ H ₇ Cl ₂ NO ₂ (256.1)	Found	51.5	2.9	27.6	5.5
				Calc.	51.6	2.8	27.7	5.5
3-Chloro.....	23	185—186°	—	Found	51.7	2.9	27.6	5.5
2,3-Dichloro.....	15	222—223°	C ₁₁ H ₆ Cl ₃ NO ₂ (290.5)	Found	45.3	2.3	36.6	4.8
				Calc.	45.5	2.1	36.6	4.8
2,5-Dichloro.....	13	145—146°	—	Found	45.4	2.2	36.6	4.8
3,4-Dichloro.....	15	193—194°	—	Found	45.4	2.2	36.5	4.9
3-Nitro.....	36	235—236°	C ₁₁ H ₇ ClN ₂ O ₄ (266.7)	Found	49.0	2.6	13.0	10.3
				Calc.	49.4	2.6	13.3	10.5

there for 1 hour. The mixture turned dark brown, and a dark precipitate was formed. At this point a total amount of about 210 ml of sodium hydroxide solution had been added. The mixture was cooled to room temperature, and evaporated to dryness under vacuum from a water bath. 99% ethanol was added, and again evaporated to remove traces of water. The remaining dark cake was extracted with dioxane in a Soxhlet apparatus. Evaporation of the dioxane extract to dryness, and sublimation (150°, 0.5 mm) gave 16.5 g of slightly yellow crystals, which after two crystallizations from ethanol-water (1:4) gave 12.4 g (15%) of XXV. The product showed no well-defined melting point. [Found: C 37.3; H 2.8; Cl 22.2; N 8.7. Calc. for C₅H₄ClNO₃ (161.6): C 37.2; H 2.5; Cl 22.0; N 8.7]. The product gave a red ferric chloride reaction.

5-Chloro-1,3-dihydroxy-2(1H)-pyridone (XXVI). A solution of XX (100 ml, 0.100 mole) was brought to pH 2.5 by dropwise addition of 40% sodium hydroxide solution (about 21 ml) at 0°. Hydroxylamine hydro-

chloride (7.0 g, 0.10 mole) was added in one portion. The mixture was heated to 75°, and kept there for 2 hours. The dark brown reaction mixture was cooled to room temperature, and brought to pH 4.0 with 40% sodium hydroxide solution (about 15 ml). During this neutralization a black tar was precipitated together with some crystalline material, and stirring became difficult. The mixture was continuously extracted with ether for 3 days. Evaporation of the ethereal extract, and sublimation of the residue (150°, 0.5 mm) gave 3.85 g of slightly yellow crystals. Crystallization from water gave 2.70 g (17%) of XXVI. [Found: C 37.1; H 2.4; Cl 21.8; N 8.5. Calc. for C₅H₄ClNO₃ (161.6): C 37.2; H 2.5; Cl 22.0; N 8.7]. The product showed no well defined melting point, but decomposed slowly above 180°. The IR spectrum was radically different from that of XXV. Another crystallization did not change the analytic values. The product gave a strong red ferric chloride reaction.

4-Chloro-1-(dimethylamino)-3-hydroxy-2(1H)-pyridone (XXVII). A solution of XX (500 ml, 0.500 mole) was brought to pH 3 by dropwise addition of 40% sodium hydroxide solution (110 ml) at 0°. A solution of N,N-dimethylhydrazine (30 g, 0.50 mole) and concentrated hydrochloric acid (50 ml) in water (250 ml) was added in one portion. The temperature of the clear mixture rose to about 10°, and the colour turned red. The mixture was heated to 85°, and kept there for 2 hours. The colour hereby changed from dark red into brown, and some black material was precipitated. The mixture was cooled to 20°, stirred at this temperature for 10 min., and filtered. The dark precipitate on the filter was washed with water, until the washings only gave a faint blue colour on addition of a solution of ferric chloride. The pH of the combined filtrate and washings was adjusted to 6.3 by dropwise addition of 40% sodium hydroxide solution (85 ml), and the mixture continuously extracted with ether overnight. Evaporation of the ethereal extract to dryness gave 21.7 g of a brownish crystalline residue. Crystallization with carbon black (1.25 g) from ethanol-water (1:2) (100 ml) gave 14.6 g of slightly brown needles of XXVII, m.p. 132–135°. Two further crystallizations from ethanol-water (1:2) gave 11.0 g (12%) of constant melting material (m.p. 135–137°). [Found: C 44.1; H 4.8; Cl 18.8; N 15.0. Calc. for C₇H₉ClN₂O₂ (188.6): C 44.5; H 4.8; Cl 18.8; N 14.9]. The product gave a strong blue ferric chloride reaction.

NMR spectra. The spectra were measured in solution in DMSO with TMS as an internal standard. 5-Chloro-3-hydroxy-2(1H)-pyridones (XXII and all ten XXIV) showed $\tau = 2.50\text{--}2.80$ for α -protons and 3.11–3.18 for

TABLE 3. τ -values for protons of 1, β -dihydroxy-2(1*H*)-pyridones.

Compound	τ for protons in positions		
	α	β	γ
VI	2.50	3.37	2.71
VII	2.54	3.81	3.15
XXV	2.50	3.66	
XXVI	2.32		3.22

γ -protons. 4-Chloro-3-hydroxy-2(1*H*)-pyridones (XXI, XXIII and XXVII) showed $\tau = 2.78-2.82$ for α -protons and $3.70-3.74$ for β -protons. Values for α -, β -, and γ -protons of 1, β -dihydroxy-2(1*H*)-pyridones are given in Table 3.

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28 Rugmarken, Farum, Denmark.

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