Tetrahedron, 1958, Vol. 3, pp. 49–61. Pergamon Press Ltd., London

STUDIES ON PYRIDOXINE AND PYRIDOXAL ANALOGS—I*

THE SYNTHESIS OF SUBSTITUTED PYRIDINEALDEHYDES

DIETRICH HEINERT and ARTHUR E. MARTELL
Department of Chemistry, Clark University, Worcester 10, Massachusetts

(*Received* 9 *December* 1957)

Abstract—The preparation, purification and properties of 3-hydroxypyridine-2-aldehyde, 3-methoxypyridine-2-aldehyde, 3-hydroxypyridine-4-aldehyde, 3-methoxypyridine-4-aldehyde and their derivatives and some new intermediates are reported. The preparation of the thio-semicarbazones of the aldehydes, as potential tuberculostatic agents, and of 3-hydroxy-4-hydroxymethylpyridine and 3-methoxy-4-hydroxymethylpyridine as pyridoxine analogs, are described.

DURING the last decade, the synthesis of a number of compounds as analogs and homologs of members of the vitamin-B_6 group has been reported.[1] All investigations on the course of vitamin-B_6 catalyzed biochemical reactions and their non-enzymatic counterparts with pyridoxine derivatives *in vitro* have led to the conclusion that the catalytically active site is a metal chelate of a Schiff base formed between an amino acid and pyridoxal(I), which in the form of a metal chelate is in equilibrium with the tautomeric Schiff base derived from pyridoxamine and a keto acid, as well as with other possible products. On this basis it seemed desirable to study the chelating properties and reactivities of a number of analogs of pyridoxal, in which only the essential hydroxyl and aldehyde groups are present. In this paper are described the synthesis of two such compounds, 3-hydroxypyridine-4-aldehyde(II) and 3-hydroxypyridine-2-aldehyde(III). In order to evaluate the influence of the 3-hydroxy groups on the stability and behavior of Schiff bases, those aldehydes with the hydroxyl group blocked by methylation(IV and V) were also prepared.

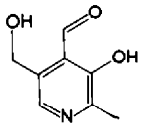
RESULTS AND DISCUSSION

The synthetic methods available for the preparation of compounds (II), (III), (IV) and (V) were limited by the fact that all *C*-substitution aldehyde synthetic procedures developed for aromatic compounds have failed to work for pyridine derivatives. Pyridine-2-aldehyde and -4-aldehyde have been obtained in only low yields by ozonolysis of benzylidenepicolines,[2,3,4,5,6] by oxidation of picolines with selenium dioxide[7] or by the McFadyen–Stevens method.[8,9,10] The Rosenmund reduction of

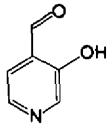
* This investigation was supported by a research grant A-1307 from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

[1] D. E. Metzler, M. Ikawa and E. E. Snell, *J. Amer. Chem. Soc.* **76**, 648 (1954).
[2] J. P. Wibaut, E. C. Kooyman and H. Boer, *Rec. Trav. Chim. Pays-Bas* **64**, 30 (1945).
[3] L. C. Craig and M. Hixon, *J. Amer. Chem. Soc.* **53**, 4369 (1931).
[4] C. E. Kaslow and R. D. Stayner, *J. Amer. Chem. Soc.* **67**, 1716 (1945).
[5] G. H. Lenart, *Ber. Dtsch. Chem. Ges.* **47**, 808 (1914).
[6] C. Harries and G. H. Lenart, *Liebigs Ann.* **410**, 95 (1915).
[7] M. Henze, *Ber. Dtsch. Chem. Ges.* **67**, 750 (1934).
[8] P. Dayson and D. L. Hammick, *J. Amer. Chem. Soc.* **61**, 781 (1939).
[9] L. Panizzon, *Helv. Chim. Acta* **24**, 24E (1941).
[10] C. Niemann, R. N. Lewis and J. T. Hays, *J. Amer. Chem. Soc.* **64**, 1678 (1942).

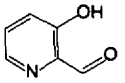
unsubstituted acid chlorides was unsuccessful,[9,11,12,13] although it proved satisfactory for the preparation of chlorinated aldehydes. The vapor-phase oxidation of the picolines described by Matthes *et al.*[14] is applicable only to volatile materials. Although pyridoxal and its homologs have been prepared from pyridoxine by mild oxidation



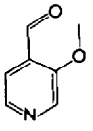
I



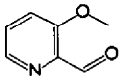
II



III



IV



V

with manganese dioxide[15–20] or (in low yield) with potassium permanganate,[21] such methods have not been employed successfully for the simple pyridinealdehydes. The procedures employed in this investigation are an improved method of oxidation with manganese dioxide and a modification of the reaction described by Wibaut and co-workers[22,23] between orthoformic esters and pyridylmagnesium compounds, and a modification of lead tetra-acetate oxidation of pyridinemethanols described by Micovic and Mihailovic.[24]

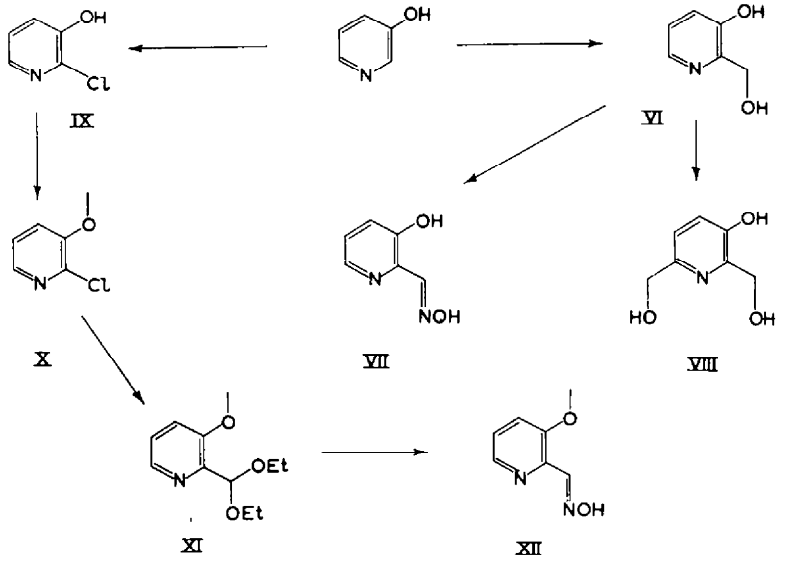
Pyridine-2-aldehydes

Although none of the four aldehydes reported in this paper have been described previously, two derivatives of 3-hydroxypyridine-2-aldehyde(III) have been reported. Kuhn and Hensel[25] oxidized 3-hydroxy-2-hydroxymethylpyridine and isolated an

[11] R. Graf and A. Weinberg, *J. Prakt. Chem.* **134**, 177 (1932).
[12] R. Graf and P. Lasszlo, *J. Prakt. Chem.* **138**, 231 (1933).
[13] C. A. Rojahn and J. Schulten, *Arch. Pharm. Berl.* **264**, 348 (1926).
[14] W. Matthes, W. Sauermilch and Th. Klein, *Chem. Ber.* **84**, 452 (1951).
[15] D. Heyl, *J. Amer. Chem. Soc.* **70**, 3434 (1948).
[16] M. Viscontini, C. Ebnöther and P. Karrer, *Helv. Chem. Acta* **34**, 1834 (1951).
[17] D. Heyl, E. Luz, S. A. Harris and K. Folkers, *J. Amer. Chem. Soc.* **73**, 3430 (1951).
[18] A. N. Wilson and S. A. Harris, *J. Amer. Chem. Soc.* **73**, 4693 (1951).
[19] D. Heyl, E. Luz, S. A. Harris and K. Folkers, *J. Amer. Chem. Soc.* **75**, 4079 (1953).
[20] M. Ikawa and E. E. Snell, *J. Amer. Chem. Soc.* **76**, 637 (1954).
[21] S. A. Harris, D. Heyl and K. Folkers, *J. Amer. Chem. Soc.* **66**, 2088 (1944).
[22] J. P. Wibaut and H. G. P. van der Voort, *Rec. Trav. Chim. Pays-Bas* **71**, 798 (1952).
[23] J. P. Wibaut and R. Huls, *Rec. Trav. Chim. Pays-Bas* **71**, 1021 (1952).
[24] V. M. Micovic and M. L. Mihailovic, *Rec. Trav. Chim. Pays-Bas* **71**, 970 (1951).
[25] R. Kuhn and H. R. Hensel, *Chem. Ber.* **86**, 1333 (1953).

oxime showing an intense lilac fluorescence in aqueous solution. In a similar manner, Metzler *et al.*[1] obtained an aldehyde preparation in the form of a sirup, estimated at 68 per cent pure,* and a solid 2,4-dinitrophenylhydazone. On the assumption that these investigators could not isolate the free aldehyde because of its possible sensitivity to further oxidation and self-condensation in aqueous solution, the oxidation was attempted with lead tetra-acetate in a mixture of benzene and acetic acid. Only low yields of the oxime were obtained, while the main product seemed to involve further oxidation. In order to stabilize the aldehyde by acetal formation, the oxidation was carried out with amorphous manganese dioxide in ethanol in the presence of triethyl orthoformate. In this way the free aldehyde, not the acetal, was isolated as lemon-yellow prisms with a pungent odor. The oxime(VII), prepared from the pure aldehyde, was obtained as colorless needles having only a slight blue fluorescence in aqueous solution and melting at 175–176°, 5° higher than the previously reported melting point. The 2,4-dinitrophenylhydazone had a melting point of 263·5–264·5°, more than 40° higher than that previously reported.

These deviations, which indicate that the previous compounds were not completely pure, probably result from the fact that the starting material (VI) used in the oxidation



had been obtained by the method of Urbanski,[26] which produces the 2,6-dimethanol (VIII) as well as the desired monosubstitution product. A series of experiments were therefore carried out with varying ratios of 3-pyridol to formaldehyde, but it was found that the disubstitution product was always formed, even when a large excess of pyridol was used. In all runs, the ruby coloration of the reaction mixture, which changes to green on acidification, noted by Urbanski[26] as an indication of the formation of open-chain products, was not observed. The color remained a light amber

* Recently S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.* **79**, 481 (1957) attempted the preparation of III by a different method and of V by methylation of crude III with methy *p*-toluenesulfonate. Neither one of the aldehydes was obtained in crystalline form. The oxime of V, however, previously unknown, was isolated: m.p. 198–199°; this investigation, m.p. 196–197°.

[26] T. Urbanski, *J. Chem. Soc.* 1104 (1946).

throughout the reaction, in accordance with the observations of Stempel and Buzzi.[27] The problem of separating 3-pyridol(VI) and (VIII) was finally solved by fractional precipitation with gaseous hydrogen chloride of 3-pyridol and (VI) from acetone or ethanol, followed by treatment of the solid mixture with excess of hydrochloric acid and fresh solvent, whereby only 3-pyridol goes into solution.

It is not possible to use direct methylation of (III) to obtain the methoxyaldehyde (V), since methylating agents would also react with the carbonyl group or with the tertiary nitrogen atom. On the other hand, the new compound 2-chloro-3-methoxypyridine(X), prepared in 60 per cent yield from (IX) with diazomethane, offered the possibility of synthesizing (XI) by means of a Grignard reaction. Wibaut and coworkers[22,23] have modified the Grignard synthesis so that satisfactory yields are obtained for bromopyridines in spite of the insolubility of pyridylmagnesium bromide by carrying out the reaction at higher temperature in the presence of a reactive alkyl halide. Although the applicability of this method to *ortho*-substituted chloropyridines was somewhat doubtful because of the low reactivity of the chloride (compared to bromides and iodides) as well as the steric influence of the methoxy group, the reaction with ethyl orthoformate was found to proceed satisfactorily with the formation of the diethylacetal(XI), which was obtained in 30 per cent yield after two distillations.

The starting material (IX) was prepared by a modification of the method of Schickh *et al.*,[28] which consisted in chlorinating with a mixture of boiling hydrochloric acid and hydrogen peroxide. In this investigation it was found that the use of ultraviolet light during the chlorination increased the 50 per cent yield obtained by Schickh *et al.* to over 75 per cent. The free methoxyaldehyde(V) was finally produced in 50–60 per cent yield by hydrolysis of the acetal with hydrogen chloride in an atmosphere of nitrogen. A similar attempt to prepare the hydroxyaldehyde(III), through the reaction of the magnesium alkoxide of (IX) with more magnesium and ethyl orthoformate in the presence of an additional Grignard reagent, failed because of lack of solubility of the magnesium derivative.

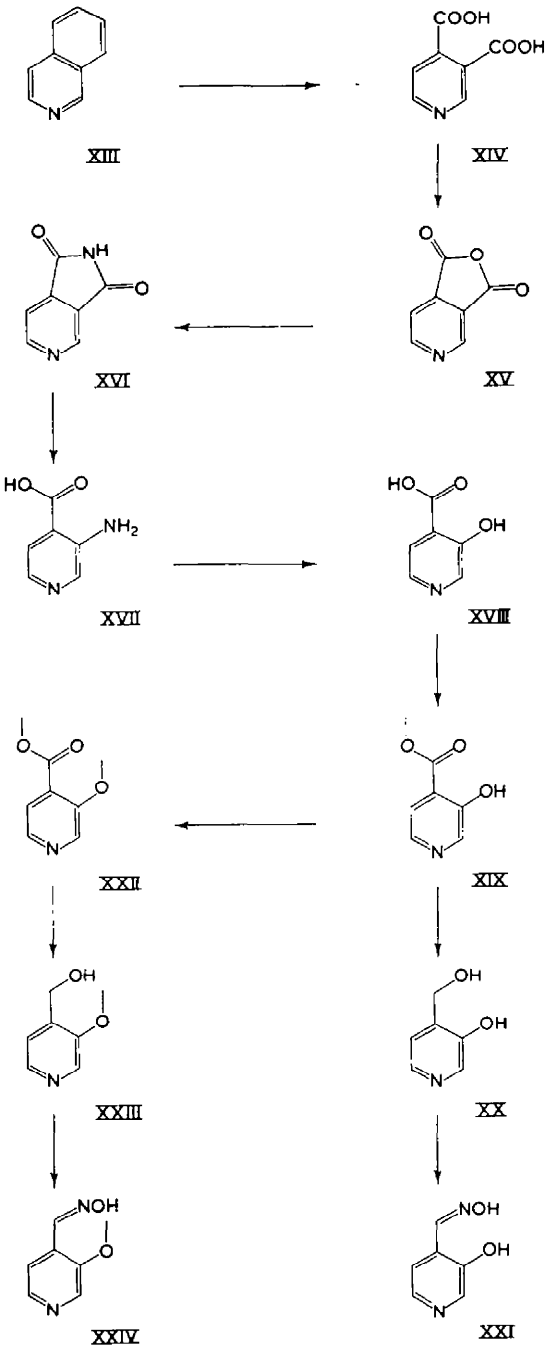
Pyridine-4-aldehydes

Of the few synthetic methods previously employed for the preparation of 3,4-disubstituted pyridines, the route outlined in the following scheme has turned out to be the least complicated. The starting material was 3-hydroxy*iso*nicotinate(XIX), which could be prepared from cinchomeronic acid(XIV) by methods reported in the literature, but which was prepared by somewhat modified procedures described under "Experimental".

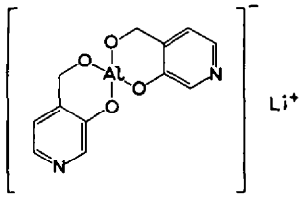
The compounds of the methoxy series were obtained by methylating (XIX) with diazomethane. This reaction proceeded much more slowly than that of the 2-chloro-3-hydroxypyridine described above, and an excess of diazomethane was needed to bring the reaction to completion. The slowness of the reaction is probably due to steric hindrance by the adjacent carboxymethyl group.

The reduction of (XXII) and (XIX) to the oxidizable pyridinemethanols was attempted with lithium aluminum hydride. While the reduction of (XXII) proceeded smoothly to give a good yield of 3-methoxy-4-hydroxymethylpyridine, the reduction of (XIX) required an excess of lithium aluminum hydride to allow the formation of the

[27] A. Stempel and E. C. Buzzi, *J. Amer. Chem. Soc.* **71**, 2969 (1949).
[28] O. V. Schickh, A. Binz and A. Schulz, *Ber. Dtsch. Chem. Ges.* **69B**, 2593 (1936).



aluminate of both hydroxyl groups. The primary reaction product of the reduction is believed to have structure (XXV). This salt was readily broken down with hydrochloric acid to give a 66 per cent over-all yield of (XX). While the methoxypyridinemethanol (XXIII) is soluble in organic solvents and was found in the ethereal layer of the reduction medium after hydrolysis, the hydroxypyridinemethanol(XX) was



XXV

found in the aqueous layer, and like its isomer (VI) is quite insoluble in ether and solvents of low polarity.

Oxidation of the pyridinemethanols was carried out as described above for 2-hydroxymethyl-3-pyridol with specially prepared manganese dioxide in ethanol. Commercial manganese dioxide was found to give only very low yields, because the crystals were not attacked by the acid. The manganese dioxide prepared by thermal decomposition of manganous carbonate was almost completely dissolved under the same reaction conditions. It is remarkable that the hydroxypyridinemethanols are more difficult to oxidize (requiring heating for 1 hr under reflux) and give much more colored side-products than the methoxypyridinemethanol(XXIII) which requires only 15 min for oxidation to the aldehyde.

The oximes (XXIV) and (XXI) as well as the corresponding thiosemicarbazones and 2,4-dinitrophenylhydrazones were isolated. The properties of the four aldehydes and their derivatives prepared in this investigation are compared in Table 1.

This work is being continued in the direction of preparing Schiff bases and metal chelates of all four pyridoxal analogs.

EXPERIMENTAL*

3-*Hydroxy*-2-*hydroxymethylpyridine hydrochloride* (VI)

To a solution of 3-pyridol (95 g, 1 mole) and sodium hydroxide (40 g) in water (400 ml), 38% formaldehyde solution (80 ml, 1 mole) was added. The clear mixture was warmed for 3 hr at 90°, then cooled to room temperature and acetic acid (60 g, 1 mole) was added. The water was removed under reduced pressure, the remaining viscous oil (or pale yellow solid) was stirred with acetone (1 l.) and the precipitated sodium acetate was filtered off. The solid was extracted with warm acetone (two 500 ml portions) and the combined extracts were further diluted with acetone (1 l.). The additional precipitate was then removed by filtration and the solution was concentrated under reduced pressure (to 1 l.). Hydrogen chloride gas was introduced at 0°, whereupon a colorless crystalline precipitate immediately formed. As soon as formation of the precipitate ceased, it was filtered off, washed with acetone (100 ml) and stirred with a saturated solution of hydrogen chloride in ethanol at 0° to dissolve unreacted pyridol. Filtration and washing with ethanol resulted in the isolation of a 45–50 per cent yield (75–80 g) of a nearly colorless solid. The product was purified by dissolving it in a minimum amount of warm water, treating with Norite, and adding a large volume of acetone at room temperature. The colorless crystals thus obtained darken above 180° and turned black at about 200°. *Anal.* Calcd. for

* All melting and boiling points are uncorrected.

TABLE 1. PHYSICAL PROPERTIES OF THE ALDEHYDES AND THEIR DERIVATIVES

Derivative	Property	(II)	(III)	(IV)	(V)
Free aldehyde	m.p.	126–128°	78–79°		55–56°
	color + form	yellow clusters	yellow clusters	colorless crystals	colorless crystals
	b.p.	—	64° (5 mm)	—	106–108°(3 mm)
Oxime	m.p.	205–206°	175–176°	160–161°	196–197°
	color + form	long colorless needles	long colorless needles	small colorless needles	short colorless rods
Thiosemicarbazone hydrochloride	m.p.	245–247° (dec.)	225–235° (dec.)	235–245° (dec.)	220–230° (dec.)
	color + form	dark-yellow leaflets	orange needles	lemon-yellow short needles	orange-yellow needles
2,4-Dinitrophenyl-hydrazone hydrochloride	m.p.	323–325° (dec.)	253–254·5° (dec.)	256–258° (dec.)	269–270° (dec.)
	color + form	yellow powder	orange powder	lemon-yellow needles	orange-yellow needles

$C_6H_7O_2N{\cdot}HCl$: C, 44·6; H, 5·0; Cl, 21·9; N, 8·7. Found: C, 44·7; H, 4·8; Cl, 22·0; N, 8·7.

3-*Hydroxypyridine-2-aldehyde* (III)

3-Hydroxy-2-hydroxymethylpyridine hydrochloride (16·2 g, 0·1 mole) and amorphous manganese dioxide (8·7 g, 0·1 mole), prepared by heating manganese carbonate for 12 hr at 300°, were suspended in ethanol (200 ml), heated with stirring to reflux temperature and 96% sulfuric acid (10·2 g, 0·1 mole) in ethanol (50 ml) was added over a period of 30 min. After additional heating under reflux for 1 hr, the black solid turned brown and the pH rose to 6. The reaction mixture was cooled to 40° and filtered. The dark yellow solution was diluted with water (200 ml) and manganous carbonate was precipitated by adding excess of sodium bicarbonate. The filtrate was extracted with ether (one 400 ml and two 150 ml portions) and the combined ether extracts were extracted with 3·7% hydrochloric acid (four 25 ml portions, containing 0·1 mole of HCl). The acidic extracts were freed from ethanol *in vacuo*, adjusted to pH 7 with sodium bicarbonate, and extracted with ether (three 100 ml portions). To the yellow extracts, dried for 12 hr over anhydrous sodium sulfate and concentrated to a small volume (40 ml), hexane (50 ml) was added and the solution,[5] treated with Norite at 50° and filtered, gave on slow cooling star-shaped clusters of yellow crystals. The yield was 40 per cent (5 g) after recrystallization from hexane and washing with ligroin (boiling range 30–60°). *Anal.* Calcd. for $C_6H_5O_2N$: C, 58·5; H, 4·1; N, 11·4. Found: C, 58·1; H, 4·1; N, 11·3.

Preparation of derivatives. A solution of the aldehyde hydrochloride, prepared as described above from the pyridinemethanol by oxidation, extraction with ether and re-extraction with diluted hydrochloric acid, was generally used for the preparation of derivatives, which were subsequently obtained in analytical pure form after one recrystallization.

3-*Hydroxypyridine*-2-*aldehyde*-2,4-*dinitrophenylhydrazone hydrochloride.* A solution of the aldehyde hydrochloride, warmed with excess of 2,4-dinitrophenylhydrazine solution in 5% hydrochloric acid, rapidly deposited a precipitate of the product. Recrystallization from a large volume of aqueous ethanol containing some hydrochloric acid resulted in the isolation of an orange powder melting at 253·5–254·5°.

3-*Hydroxypyridine*-2-*aldehyde-thiosemicarbazone hydrochloride.* A solution of the aldehyde hydrochloride (0·1 mole) was added to a slurry of thiosemicarbazide (9·1 g, 0·1 mole) in ethanol (150 ml) and acetic acid (15 ml). The intense yellow solution, after being heated under reflux for 20–30 min, deposited orange needles on cooling. Purification by recrystallization from 4% aqueous hydrochloric acid and washing the product with absolute ethanol gave orange needles that decomposed at 225–235° without melting. *Anal.* Calcd. for $C_7H_9ON_4ClS \cdot 2H_2O$: C, 31·3; H, 4·9; N, 20·8; Cl, 13·2. Found: C, 31·3; H, 4·19; N, 20·7; Cl, 13·4.

3-*Hydroxypyridine*-2-*aldoxime.* A solution of the aldehyde hydrochloride (0·1 mole), sodium acetate (15 g) and hydroxylamine hydrochloride (14 g, 0·2 mole) was warmed at 100° for 20 min. After the mixture had been set aside for 2 hr at 0° and the vessel had been scratched, the product crystallized from the reaction mixture. Recrystallization from boiling water with addition of Norite gave long colorless needles, m.p. 178–179°. *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52·2; H, 4·4; N, 20·3. Found: C, 52·0; H, 4·4; N, 19·9.

2-*Chloro*-3-*hydroxypyridine* (IX)

Into a solution of 3-pyridol (95 g, 1 mole) in 37% hydrochloric acid (585 ml, 6 moles), heated with stirring to reflux temperature, 30% hydrogen peroxide (285 ml, 2·5 moles) was dropped slowly under the ultraviolet radiation of a 140 watt lamp (Hanovia type 30,600, without filter) applied from outside the reaction vessel. After 5 min of additional heating under reflux, water was distilled off under reduced pressure until a thick slurry of orange crystals of 2-chloro-3-hydroxypyridine hydrochloride was obtained. Ammonia gas was then introduced into the suspension at 0° until the pH rose to 8, and the dark reaction mixture was extracted with ether (five 200 ml portions). The residue was filtered off and the liquid was extracted continuously with ether (500 ml) for 24 hr. The combined ether extracts, after being dried over anhydrous sodium sulfate, gave after evaporation of the ether a residue of slightly yellow crystals in 70 per cent yield (90 g), or a rapidly crystallizing oil. The product was recrystallized three times from boiling water, and the oil containing higher chlorinated products was discarded. A 25–30 per cent yield (32–40 g) of colorless needles (m.p. 164–165° in a sealed tube) was obtained. *Anal.* Calcd. for C_5H_4ONCl: N, 10·8; Cl, 27·4. Found: N, 10·8; Cl, 27·3.

2-*Chloro*-3-*methoxypyridine* (X)

To a solution of 2-chloro-3-hydroxypyridine (64·5 g, 0·5 mole) in ether (250 ml) and ethanol (100 ml), an ether solution of diazomethane (containing at least 1 mole of

CH_2N_2[29] was added dropwise to keep nitrogen evolution under control. After the reaction product had been set aside at 20° for 12 hr, the color was dark red. The solvents were removed by distillation and the remaining dark red oil, which crystallized on cooling, was extracted with boiling ether (three 200 ml portions). The combined ether solutions were washed twice with water (100 ml), dried for 12 hr over anhydrous sodium sulfate, the ether was evaporated, and the remaining pale-yellow crystals were purified by treatment with Norite and recrystallization from light petroleum boiling range 30–60°). A 50–60 per cent yield (36–43 g) of colorless flat long needles of narcotic odor were obtained, m.p. 48–49°. *Anal.* Calcd. for C_6H_6ONCl; C, 50·2; H, 4·2; N, 9·7. Found: C, 50·2; H, 4·2; N, 9·7.

3-*Methoxypyridine-2-aldehyde diethylacetal* (XI)

A solution of 2-chloro-3-methoxypyridine(X) (14·4 g, 0·1 mole) and ethyl bromide (30 g, 0·27 mole) in absolute ether (100 ml) was dropped into a vigorously stirred mixture of magnesium turnings (9·8 g, 0·4 mole), absolute ether (20 ml) and ethyl bromide (3 g, 0·03 mole), in which a Grignard reaction had been started at such a rate that the reaction proceeded at a moderate rate. After additional heating under reflux for 30 min, the main part of the ether (80 ml) was distilled off, and benzene (100 ml, dried over calcium hydride) was added to dissolve the ether-insoluble pyridylmagnesium salts. The reaction mixture was cooled to 30° and triethyl orthoformate (60 g, 0·4 mole) was added. The reaction was started by brief warming in a water bath, and maintained by dropwise addition of the orthoester. The product, which separated into two phases, was heated under reflux for 20 min with stirring, and then cooled to 30° and treated with a 30% aqueous solution of ammonium chloride (250 ml). As soon as the lower layer (dark viscous oil) had dissolved, the unreacted magnesium and some tar were removed by filtration, the benzene layer was removed, and the aqueous layer was extracted with ether (six 50 ml portions). The benzene and ether solutions were combined, dried with anhydrous sodium sulfate and extracted with 96% sulfuric acid (6 g, 0·05 mole) in water (six 25 ml portions). The extracts were washed with ether (two 100 ml portions), adjusted to pH 9 with 30% aqueous sodium hydroxide and extracted with ether (four 100 ml portions). The dried extracts (left for 12 hr in contact with anhydrous sodium sulfate) were fractionated *in vacuo*. A fraction boiling at 58° (3 mm) consisting of 3-methoxypyridine was separated from the one boiling above 100° (3 mm). Redistillation gave the pure acetal as a pale yellow oil, b.p. 120° (3 mm). The yield was 30 per cent (6·3 g) of the theoretical amount. *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62·5; H, 8·1; N, 6·6. Found: C, 62·4; H, 7·7; N, 6·8.

3-*Methoxypyridine-2-aldehyde* (V)

A solution of the diethylacetal(XI) (21·1 g, 0·1 mole) in 10% hydrochloric acid (200 ml) was heated under reflux in a nitrogen atmosphere for 1 hr. The dark-yellow solution was adjusted to pH 10 with 30% sodium hydroxide and extracted with chloroform (four 100 ml portions). The combined extracts were dried with anhydrous sodium sulfate and fractionated *in vacuo*, when a 50–60 per cent yield (7–8 g) of a pale yellow oil, b.p. 106–108° (3 mm), which crystallized on cooling, was obtained. Recrystallization from benzene gave colorless leafets, m.p. 55–56°. *Anal.* Calcd. for $C_7H_7O_2N$: C, 61·3; H, 5·2; N, 10·2. Found: C, 61·9; H, 5·8; N, 9·8.

[29] B. Eistert, *Neuere Methoden der Organischen Chemie*. Verlag Chemie (1948).

Preparation of derivatives of (V). A solution of the aldehyde hydrochloride obtained by hydrolysis of the diethylacetal gave analytically pure derivatives in procedures similar to those described above.

2,4-*Dinitrophenylhydrazone hydrochloride of* (V). By means of the general procedure described above for (III), an orange-yellow crystalline powder, m.p. 269–270°, was obtained.

Thiosemicarbazone hydrochloride of (V). By the procedure described above for (III), orange-yellow needles, m.p. 220–230° (dec.), was obtained in 80–90 per cent yield. *Anal.* Calcd. for $C_8H_{11}ON_4ClS$: C, 38·9; H, 4·5; N, 22·7. Found: C, 38·8; H, 4·5; N, 23·1.

Thiosemicarbazone of (V). The concentrated aqueous solution of the hydrochloride obtained by the general procedure described above for (III) was warmed with sodium acetate and adjusted to pH 6 with sodium bicarbonate. Addition of ethanol and cooling produced yellow crystals, which were recrystallized from aqueous 10% ethanol to give a 50 per cent yield, m.p. 204–205° (dec.). *Anal.* Calcd. for $C_8H_{10}ON_4S$: C, 45·7; H, 4·8; N, 26·7· Found: C, 45·6; H, 4·6; N, 27·0.

3-*Methoxypyridine*-2-*aldoxime*(XII). The *oxime* prepared as described above for (III) was obtained as a 55 per cent yield of short colorless needles, m.p. 196·5–197·5°. *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55·2; H, 5·3; N, 18·4. Found: C, 55·2; H, 5·3; N, 18·4·

Pyridine-3,4-*dicarboxylic acid* (XIV)[30] (*cinchomeronic acid*)

*iso*Quinoline (129·2 g, 1 mole) was oxidized with 96·5% sulfuric acid (1350 g, 10 moles and 33 per cent excess), with selenium (2·4 g, 0·03 mole) as catalyst. For this operation, sulfuric acid (750 g) was heated with powdered selenium (1·4 g) in a three-necked flask provided with a stirrer, thermometer, dropping funnel and an air condenser connected to a wide gas-outlet tube to dispose of the sulfur dioxide and water produced in the reaction. The selenium dissolved completely as soon as the temperature reached 280°. Powdered selenium (1 g) was dissolved in 96% sulfuric acid (50 g) by heating and stirring at 250° for a few minutes, and the resulting green solution was allowed to cool down to 30° and was then added to the cooled solution of the *iso*quinolime (129·2 g) in 96% sulfuric acid (550 g). The mixture thus obtained was dropped into the heated and stirred sulfuric acid at such a rate that the temperature was maintained between 270 and 280°. After completion of the addition, the reaction mixture was kept at 280° for 1 hr. It was then allowed to cool down and the viscous reaction product was poured over crushed ice (400 g). The solution thus obtained was boiled for 5 min with activated carbon (5 g), the carbon and selenium were removed, and the cooled filtrate was brought to pH 1·5 by addition of 29% aqueous ammonia. The precipitate cinchomeronic acid was washed with a large amount of water and dried at 110° to give a 60 per cent yield (100 g) of a white amorphous powder, m.p. 256°.

Pyridine-3,4-*dicarboxylic acid imide* (XVI) (*cinchomeronimide*)

The imide (XVI) was prepared in 70–85 per cent yield from the anhydride (XV),[31] or better without isolation of (XV),[32] and was recrystallized once from acetic acid.

[30] M. B. Mueller, *U.S. Pat.* 2,436,660 (1948); *Chem. Abstr.* **42**, 4203 H (1948).
[31] G. B. Bachman and R. S. Barker, *J. Org. Chem.* **14**, 97 (1949).
[32] K. C. Blanchard, E. H. Dearborn, L. C. Lasagna and E. L. Buhle, *Bull. Johns Hopkins Hosp.* **91**, 330 (1952).

3-*Aminopyridine-4-carboxylic acid* (XVII)

The amino acid (XVII) was obtained in 55 per cent yield from (XV) by the method of Blanchard *et al.*[32]

3-*Hydroxypyridine-4-carboxylic acid* (XVIII)

The amino group of (XVII) was converted to hydroxyl in 65 per cent yield.[32] The product was recrystallized from a large volume of boiling water with the addition of Norite.

3-*Hydroxypyridine-4-carboxylic acid methyl ester* (XIX)

3-Hydroxypyridine-4-carboxylic acid(XVIII) (139·1 g, 1 mole) was heated under reflux with a mixture of methanol (220 ml, 7 moles), 96·5% sulfuric acid (152 g, 1·5 mole) and 1,2-dichloroethane (480 ml) for 20 hr. The unreacted acid was precipitated from the cooled reaction mixture on dilution with water (600 ml) and was recovered by filtration (42 g). The filtrate was neutralized with sodium bicarbonate and extracted with chloroform (six 150 ml portions). The combined extracts were dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. The crystalline residue that remained (83 g, 85 per cent yield based on the hydroxy acid) was purified by recrystallization from light petroleum (800 ml, boiling range 60–110°), when pale-yellow thick crystals of aromatic odor were obtained. (75 g, m.p. 79–80°, in agreement with the literature[33]).

3-*Methoxypyridine-4-carboxylic acid methyl ester* (XXII)

A solution of diazomethane in ether (containing at least 1 mole of CH_2N_2) was added all at once to a solution of 3-hydroxypyridine-4-carboxylic acid methyl ester (XIX) (153·1 g, 1 mole) in ether (3 l.). After addition of ethanol (125 ml), the reaction began slowly with gas development and deepening of color. After the mixture had been set aside for 12 hr at room temperature, the solvents were removed under reduced pressure, and the dark red oily product that crystallized on cooling was extracted with boiling hexane (2 l.). After treatment with Norite, the yellow solution deposited colorless crystals and some oil. After repeated crystallizations from hexane, a 70 per cent yield (117 g) of short colorless needles, m.p. 55–56°, was obtained. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57·5; H, 5·4; N, 8·4. Found: C, 57·3; H, 5·5; N, 8·1.

3-*Hydroxy-4-hydroxymethylpyridine hydrochloride* (XX)

A solution of 3-hydroxypyridine-4-carboxylic acid methyl ester (XIX) (15·3 g, 0·1 mole) in ether (250 ml, dried over lithium aluminum hydride) was dropped slowly with stirring into a suspension of lithium aluminum hydride (8·5 g, 0·23 mole) in ether (250 ml, dried over lithium aluminum hydride). After the initial violent reaction, in which a thick precipitate formed, had slowed down, the mixture was warmed to reflux temperature for 10 min and was then cooled to room temperature. Ethyl acetate (27 g) was added dropwise in order to destroy the excess of hydride, and water (20 ml) was subsequently added to decompose the lithium alkoxides. The reaction mixture was filtered, and the solid obtained was extracted with boiling ethanol (two 250 ml portions) and then with boiling water (two 250 ml portions). The aqueous extracts were combined and adjusted to pH 4 by the addition of acetic acid, the water

[33] H. H. Fox, *J. Org. Chem.* **17**, 547 (1952).

was distilled off *in vacuo*, and the oily slowly crystallizing residue was dissolved in a mixture of ethanol (50 ml) and acetone (500 ml). Acetone was added until precipitation of lithium acetate was complete, and the yellow solution was filtered and concentrated *in vacuo* (to 500 ml), and the hydrochloride was precipitated with hydrogen chloride gas at 0°. The fine crystalline product was filtered off, washed with acetone and purified by being dissolved in water (15 ml), Norite (1 g) added, and precipitated with acetone (1200 ml). A 66 per cent yield (10·7 g) of pale-yellow leaflets was obtained, m.p. 198–202°. *Anal.* Calcd. for $C_6H_8O_2ClN$: C, 44·6; H, 5·0; Cl, 21·9; N, 8·7. Found: C, 44·5; H, 4·8; Cl, 22·0; N, 8·6.

3-*Methoxy*-4-*hydroxymethylpyridine* (XXIII)

A solution of 3-methoxypyridine-4-carboxylic acid methyl ester(XXII) (16·7 g, 0·1 mole) in ether (250 ml, dried over lithium aluminum hydride) was added dropwise in the course of 1 hr to a suspension of lithium aluminum hydride (9·5 g, 0·25 mole) in ether (250 ml, dried), which had been stirred for 10 min in a nitrogen atmosphere. A white precipitate formed locally, but when the mixture was stirred it dissolved almost completely in the lithium aluminum hydride solution. While the mixture was being cooled with ice-water, ethyl acetate (35·2 g, 0·4 mole) was added to destroy the excess of hydride. The lithium compounds were decomposed by adding cold water (18 ml, 1 mole) and the ethereal solution was separated from the hydroxide precipitate by filtration. The solid was extracted twice with ether (100 ml) and the combined ether solutions, after being dried with anhydrous sodium sulfate for 5 hr, were evaporated under reduced pressure. The remaining yellow oil, which crystallized completely on cooling, was purified by extraction with hexane in a continuous extractor. Most of the product was obtained in the form of colorless crystals in the extraction flask, while the solvent deposited only a small amount of substance on cooling, and the dark-red tarry impurities remained in the extraction thimble. A 46–50 per cent yield (6·4–7·0 g) of pale yellow crystals, soluble in water, ethanol, ether and hot benzene, but insoluble in ligroin (boiling range 30–60°) and cold hexane, was obtained, m.p. 113–114° (after recrystallization from benzene–hexane). *Anal.* Calcd. for $C_7H_9O_2N$: C, 60·4; H, 6·5; N, 10·1. Found: C, 59·9, H, 6·5; N, 9·7.

The hydrochloride, m.p. 206–207°, was obtained as colorless crystals in 80 per cent yield by addition of ethanolic hydrogen chloride to a solution of (XXIII) in ethanol at 0°.

3-*Hydroxypyridine*-4-*aldehyde* (II)

A suspension of 3-hydroxy-4-hydroxymethylpyridine hydrochloride(XX) in ethanol was oxidized and treated as described above for the isomeric 2-aldehyde(III). A yield of 30–40 per cent of yellow clusters of short crystals, m.p. 126–128°, was obtained. *Anal.* Calcd. for $C_6H_5O_2N$: C, 58·5; H, 4·1; Found: C, 58·0; H, 4·4.

2,4-*Dinitrophenylhydrazone hydrochloride of* (II). The oxime was obtained as a yellow crystalline powder, m.p. 323–325° (dec.), by the general procedure described above.

Thiosemicarbazone hydrochloride of (II). Small dark yellow leaflets of the *thiosemicarbazone* were obtained in 30 per cent yield, m.p. 245–247° (dec.), by the general procedure described above for (III). *Anal.* Calcd. for $C_7H_9ON_4ClS$; C, 36·1; H, 3·9; N, 24·1; Cl, 15·2. Found: C, 35·9; H, 3·9; N, 24·1; Cl, 15·2.

3-*Hydroxypyridine-4-aldoxime* (XXI). The *oxime* was obtained in 30 per cent yield as long colorless needles, m.p. 205–206°, by the general procedure described above. *Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52·5; H, 4·4; N, 20·3. Found: C, 51·8; H, 4·4; N, 19·5.

3-*Methoxypyridine-4-aldehyde* (IV)

A suspension of the hydrochloride of 3-methoxy-4-hydroxymethylpyridine(XXIII) in ethanol was oxidized and processed as described above for (III). A 60 per cent yield of colorless crystals was obtained. *Anal.* Calcd. for $C_7H_7O_2N$: C, 61·3; H, 5·2. Fount: C, 61·9; H, 5·6.

2,4-*Dinitrophenylhydrazone hydrochloride of* (IV). The 2,4-dinitrophenylhydrazone was obtained as described above for (III) in 60 per cent yield as lemon-yellow needles, which were recrystallized from hot water, m.p. 256–258° (dec.).

Thiosemicarbazone hydrochloride of (IV). The *thiosemicarbazone* prepared by the procedure described for (III) was obtained as lemon-yellow needles, almost insoluble in ethanol, m.p. 235–245° (dec.). *Anal.* Calcd. for $C_8H_{11}ON_4ClS$: C, 38·9; H, 4·5; N, 22·7; Cl, 14·4. Found: C, 39·1; H, 4·5; N, 22·7; Cl, 14·3.

3-*Methoxypyridine-4-aldoxime*(XXIV). The *aldoxime* was obtained in 75 per cent yield as colorless needles, m.p. 160–161°, by the procedure described above for the oxime of (III). *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55·3; H, 5·3; N, 18·4. Found: C, 55·1; H, 5·3; N, 18·6.