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THE SYNTHESIS OF SOME INTERMEDIATES FOR USE IN THE PREPARATION OF ANALOGS OF SALICYLALDEHYDE ETHYLENEDIIMINE COBALT ("SALCOMINE")[1]

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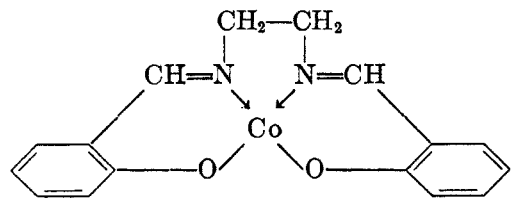
As part of a study having for its object the examination of the oxygen-carrying properties of chelate compounds of the type exemplified by salicylaldehyde ethylenediimine cobalt ("Salcomine") (I)



I

a large number of substances were prepared and tested in an effort to determine the structural requirements for activity and to discover chelates with oxygen-carrying properties superior to those of I. Among the practical improvements sought were (a) greater stability than Salcomine in repeated passage through the cycle of oxygenation and deoxygenation; (b) greater oxygen capacity (over the capacity of one atom of oxygen per mole of chelate possessed by Salcomine); and (c) increased rates of oxygenation and deoxygenation under conveniently attainable temperature and pressure conditions.

In pursuing these objectives modifications were made in the structure of I by using polyamines other than ethylenediamine, using substituted salicylaldehydes or other substances of related structures, and using other metals in place of cobalt. Most of the substances used in preparing the many analogs of I studied were well-known compounds, many of them prepared in this laboratory by established methods.[2] In a number of cases, however, compounds hitherto unreported were required. The syntheses of a number of these are described in this paper.

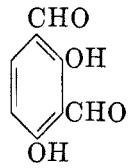
One of the ends sought in this work was to increase the proportion of metal in the complexes and thus to increase the percentage yield of oxygen obtained when these substances are used as reversible oxygen carriers. One of the possible means to this end was to use in place of salicylaldehyde compounds containing two *o*-hydroxyaldehyde groupings per benzene nucleus. Only one such com-

[1] The work described in this paper was carried out as part of a program of research under Division 11, Section 1, of the National Defense Research Committee, under a contract between the Office of Scientific Research and Development and the University of California.

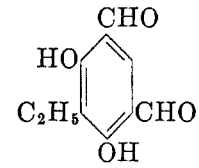
[2] All of the final chelate compounds were prepared and tested in other laboratories, with which we collaborated. Presumably much of this work will be reported elsewhere.

pound, resorcinol-2,4-dialdehyde (II) has been described previously (1, 2), and another representative of this class of compounds has been prepared in the present work. The new compound, 2,4-dihydroxy-3-ethylisophthalaldehyde (III) differs from I in that it possesses a symmetrical, and not vicinal, arrangement of the hydroxyl and aldehyde functions.

2,4-Dihydroxy-3-ethylisophthalaldehyde was prepared by the formylation of 2-ethylresorcinol, chloromethylation of the dimethyl ether of the latter, conversion of the chloromethyl group to a formyl group (by two methods), and finally demethylation.



II



III

While it would have been desirable to prepare the more immediate analog of II, lacking the ethyl group, the presence of a group at the 3-position was necessary to direct the entering chloromethyl group to the 5-position in 2,4-dimethoxy-3-ethylbenzaldehyde. The ethyl group was chosen because of the ready availability of 2-ethylresorcinol (3, 4).

In preparing II for tests of chelates derived from it, it was found impossible to duplicate the yield of 25% reported by Shoesmith and Haldane (1). After a study of the condensation of resorcinol and diphenylformamidine it was found possible to obtain reproducible yields of 14%, but no higher yield was obtained in any of numerous experiments.

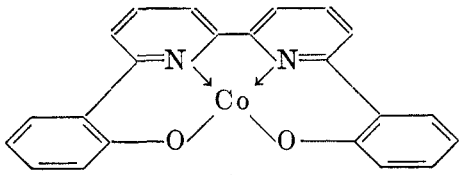
Since the degradation of Salcomine, when it is used as a reversible oxygen carrier, takes place at least in part as a result of oxidative attack on the salicylaldehyde nucleus, it was hoped that the use of a heterocyclic *o*-hydroxyaldehyde would permit the formation of an active but more stable cobalt complex. Experiments along this line were carried far enough to indicate that complexes containing such heterocyclic substances were devoid of oxygen-carrying activity.

Because of the limitations imposed by the exigencies of the program only a limited number of the possible avenues of approach to compounds of the type sought could be explored. Two methods were examined, and led to a sufficient number of substances for testing as chelates with ethylenediamine and cobalt. In view of the lack of oxygen-carrying ability in the compounds studied in these preliminary tests, the work was not extended further.

The most direct approach to the preparation of heterocyclic *o*-hydroxyaldehydes appeared to be the use of the Reimer-Tiemann reaction with suitable hydroxy compounds. Conrad and Limpach (5) have reported the preparation of 3-formyl-4-hydroxyquinaldine by this method, and in the present work this method was extended to the preparation of other 3-formyl-4-hydroxyquinaldines. Attempts to introduce a formyl group by this procedure into 4-hydroxypyridine and 4-hydroxy-2,6-dimethylpyrimidine were unsuccessful.

A second method investigated was the MacFayden-Stevens reaction (6, 7) starting from heterocyclic *o*-hydroxycarboxylic acids. This method proved of value in one case, and by its means was prepared 2-hydroxy-3-formyl-4,6-dimethylpyridine. An attempt to prepare in this way a 4-hydroxy-5-formyl-2-methylpyrimidine failed.

A number of compounds were prepared in which the role of the Schiff's-base nitrogen atoms in I was filled by the nitrogen atoms of heterocyclic nuclei. The substances chosen for study were 2-*o*-hydroxyphenylpyridine, 2-*o*-hydroxyphenylquinoline, 1-*o*-hydroxyphenylisoquinoline and 6,6′-bis-(*o*-hydroxyphenyl)-2,2′-dipyridine (IV). The latter compound was of special interest because the cobalt complex prepared from it closely resembles I in its molecular architecture.

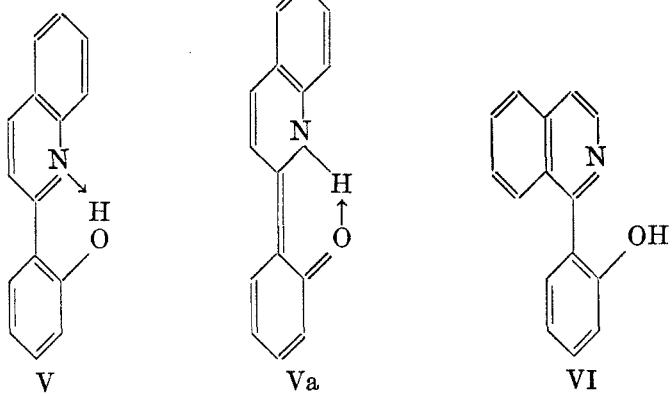


IV

This close resemblance is strikingly shown by the close similarity between molecular models (Stuart) of I and IV.

All of these substances were prepared by the addition of *o*-methoxyphenyllithium to the appropriate nitrogen heterocycle, followed by oxidation of the first-formed dihydro compound with nitrobenzene and demethylation with hydrobromic acid.

It is interesting to note that while 2-*o*-hydroxyphenylquinoline (V) is yellow, 1-*o*-hydroxyphenylisoquinoline (VI) is a colorless compound. Since the color of the first can be ascribed to the participation of resonance forms arising from Va, the isoquinoline derivative is probably inhibited from undergoing this kind of resonance by the steric interference of the 8-position of the heterocyclic nucleus.



V Va VI

An additional observation made in the course of these studies is worthy of comment. When phenyllithium was added to pyridine and to quinoline under

mild conditions and the products isolated without an intermediate oxidation by nitrobenzene, attempts to prepare picrates of the dihydro compounds thus prepared resulted in the production of picrates of the fully aromatic compounds; and the solutions in which picrate formation was taking place acquired intense red colorations during the course of the reactions. Treatment of the previously aromatized (by nitrobenzene) compounds with picric acid yielded the same picrates as were produced from the dihydro compounds, but no unusual colorations appeared in the solutions. Bergmann, Blum-Bergmann, and v. Christiani (8) reported that the reaction of phenyllithium with isoquinoline yielded what they considered to be 1-phenylisoquinoline, m.p. 80°, which formed a picrate, m.p. 165°. Ziegler and Zeiser (9), on the other hand, treated the product from the reaction of phenyllithium and isoquinoline with nitrobenzene and obtained what was probably 1-phenylisoquinoline, m.p. 97°. It appears likely that Bergmann's compound, m.p. 80°, was 1-phenyl-1,2-dihydroisoquinoline, and that his picrate was that of 1-phenylisoquinoline.

EXPERIMENTAL

Resorcinol-2,4-dialdehyde. The following experiments are typical of a number that were run in attempts to obtain the yield of 25% reported for this compound (1). Method B was found to give yields of 14% in larger runs than the one described.

A. A mixture of 5.0 g. of resorcinol and 9 g. of diphenylformamidine was heated to 175° for 15 minutes. The melt was cooled somewhat and poured into 50 ml. of 6 *N* sodium hydroxide and the mixture steam distilled until no more aniline came over. The residue was acidified and steam distillation was resumed until no more solid came over. The resinous residual material was removed, boiled for 10 minutes with 6 *N* sodium hydroxide, acidified and again subjected to steam distillation. The solid product in the distillate was collected and dried. The yield was 0.65 g. (9%) of nearly pure dialdehyde.

B. After the fusion of 5.0 g. of resorcinol and 9.0 g. of diphenylformamidine as described above, 100 ml. of alcohol was added to the cooled melt and the mixture boiled for several minutes. The insoluble residue (a), the material which separated from the solution on cooling (b), and the material precipitated by dilution of the filtrate (c) were separately boiled with 50 ml. of 6 *N* sodium hydroxide, acidified, and steam distilled.

Dialdehyde was obtained from (c) only, 1.17 g. (14%) being isolated from the steam distillate. The compound crystallized from dilute alcohol as soft, yellowish-white needles, m.p. 127–128° [reported (1), 126°].

Anal. Calc'd for $C_8H_6O_4$: C, 57.9; H, 3.6.
Found: C, 57.8; H, 3.8.

2-Ethylresorcinol was prepared by the method described by Russell (3, 4).

2-Ethyl-4-resorcylaldehyde. A stirred mixture of 10.2 g. of 2-ethylresorcinol, 12.0 g. of zinc cyanide, and 150 ml. of dry ether was saturated with dry hydrogen chloride. The gas stream was discontinued 30 minutes after saturation, the ether layer decanted, and the solid residue boiled with 150 ml. of water. Sufficient alcohol was added to the hot solution to bring about complete solution, and on cooling a first crop of 4.8 g. of product separated. An additional 5.3 g. was obtained from the mother liquor. The total yield (10.1 g.) was 75% of material melting at 118.5–120° [reported (10) 115–118°]. Yields of 74–80% were obtained in other runs.

2-Ethyl-4-resorcylaldehyde dimethyl ether. To a well-stirred solution of 4.5 g. of 2-ethyl-4-resorcylaldehyde in 25 ml. of methanol were added alternately in small portions a solution of 50 g. of potassium hydroxide in 300 ml. of water, and 60 ml. of dimethyl sulfate. Refluxing was maintained during the addition. After acidification, the methanol was removed

by distillation and the residue extracted with ether and the ether solution washed with dilute alkali. Removal of the ether left 4.1 g. (81%) of the dimethyl ether, m.p. 58–59.5°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2; OCH_3, 32.0.
Found: C, 67.6; H, 7.4; OCH_3, 31.8.

In another run, there was also isolated the monomethyl ether, 3-ethyl-4-methoxysalicylaldehyde, m.p. 47–48°, from petroleum ether.

Anal. Calc'd for $C_{10}H_{12}O_3$: OCH_3, 17.2. Found: OCH_3, 16.9.

2,4-Dimethoxy-3-ethyl-5-chloromethylbenzaldehyde. A mixture of 13.5 g. of 2-ethyl-4-resorcylaldehyde dimethyl ether, 27 ml. of 40% formalin and 10 g. of zinc chloride was stirred vigorously while hydrogen chloride was passed in. Sufficient external heat was applied to keep the mixture refluxing. After 90 minutes the mixture was poured onto ice and the oil which separated taken up in ether. The solution was washed thoroughly with sodium bicarbonate solution and water, dried, and the ether removed. Distillation of the residual oil gave 14.4 g. (92%) of material boiling at 166–166.5°/4 mm., which solidified on standing. A sample recrystallized from dilute alcohol formed stout white needles, m.p. 49–50°.

Anal. Calc'd for $C_{12}H_{15}ClO_3$: C, 59.4; H. 6.2; OCH_3, 25.6.
Found: C, 59.2; H, 6.5; OCH_3, 25.4.

4,6-Dimethoxy-5-ethylisophthalaldehyde. (A) A mixture of 14.5 g. of the chloromethyl compound, 21 g. of hexamethylenetetramine, 150 ml. of alcohol, and 50 ml. of water was refluxed for 3 hours. The alcohol was evaporated, 50 ml. of 6 *N* sulfuric acid added, and the mixture extracted with ether. From the ether extract there was obtained, after recrystallization from dilute alcohol and then from ligroin, 4.7 g. (35%) of the dialdehyde, m.p. 96–97°.

(B) The chloromethyl compound (23.0 g.) was converted to the acetoxymethyl derivative by refluxing it for 18 hours with 25 g. of anhydrous potassium acetate in 140 ml. of glacial acetic acid. The solvent was removed under reduced pressure, the residue mixed with water and neutralized with potassium carbonate and the acetoxymethyl aldehyde extracted with ether. Removal of the ether left 25 g. of crude acetoxymethyl compound, which was converted directly into the carbinol by treatment for 30 min. with 200 ml. of methanol containing about 0.05 mole of sodium methoxide. There was obtained 21.5 g. of the crude carbinol.

The carbinol was added slowly to 250 ml. of concentrated nitric acid (11). The temperature rose to 50°; after 15 minutes the solution was poured into 750 ml. of ice-water. The solid which separated was collected, washed with sodium bicarbonate solution and with water. Ether extraction of the aqueous solution afforded an additional amount. The dialdehyde (9.4 g.; 45%) was crystallized from alcohol; m.p. 95–96°.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4; OCH_3, 27.9.
Found: C, 64.8; H, 6.5; OCH_3, 27.8.

4,6-Dihydroxy-5-ethylisophthalaldehyde. A mixture of 12.0 g. of 4,6-dimethoxy-5-ethylisophthalaldehyde, 40 ml. of 48% hydrobromic acid, and 40 ml. of water was boiled under reflux for 4 hours. The solution was poured onto ice, made alkaline, and washed with ether to remove undemethylated material, then acidified and the oil which separated taken up in ether. The crude material, obtained on removal of the ether, was purified by sublimation at 145–150°/3–4 mm. The product formed nearly colorless prisms, m.p. 104–106°; yield, 7.0 g. (67%).

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.9; H, 5.3; OCH_3, 0.00
Found: C, 61.5; H, 5.3; OCH_3, 0.2.

3-Cyano-4,6-dimethyl-2-pyridone was prepared by he method of Bardhan (12).

Ethyl, 4-6-dimethyl-2-pyridone-3-carboxylate was prepared according to Simonsen and Naik (13). The yields in this reaction left much to be desired, and it was deemed preferable to proceed to the hydrazide through the hydrolysis of 3-cyano-4,6-dimethyl-2-pyridone to the amide (14), followed by treatment of the amide with hydrazine as detailed below.

4,6-Dimethyl-2-pyridone-3-carboxhydrazide. (A) From the ester: A solution of 4.35 g. of ethyl 4,6-dimethyl-2-pyridone-3-carboxylate in 5 ml. of 85% hydrazine hydrate was refluxed for three hours. A clear solution resulted when the solution was first heated to

150°, but after about one and one-half hours a precipitate began to appear. To the cooled reaction mixture was added 10 ml. of absolute alcohol, the lumps were crushed and the solid collected. The mother liquor was distilled with xylene until the water was removed, the solid residue collected and washed with absolute alcohol.

The total yield was 3.5 g. (86%). The hydrazide crystallized from absolute alcohol as soft, white needles, m.p. 239–240°.

Anal. Calc'd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12.
Found: C, 53.18; H, 6.22.

(B) From the amide: The direct replacement of $-NH_2$ by $-NHNH_2$ was found to occur satisfactorily. Although it was difficult to prepare pure hydrazide by this method it was found easy to prepare a pure sample of the benzenesulfonyl derivative of the hydrazide from a sample contaminated with amide.

A solution of 30.0 g. of 4,6-dimethyl-2-pyridone-3-carboxamide in 50 ml. of alcohol and 15 ml. of 85% hydrazine hydrate was heated in an oil-bath, allowing the alcohol to distil off. After the addition of another 10 ml. of hydrazine hydrate the solution was heated for an hour at 140–150°. The mixture was cooled and the product collected and recrystallized from alcohol. There was obtained 15.0 g. of hydrazide suitable for conversion into the benzenesulfonyl derivative.

Benzenesulfonyl 4,6-dimethyl-2-pyridone-3-carboxhydrazide. To a solution of 1.10 g. of the hydrazide in 25 ml. of warm pyridine was added 0.85 ml. of benzenesulfonyl chloride. A crystalline precipitate formed at once. The mixture was heated until a clear solution resulted and water was added until crystallization began. The product which separated on cooling was collected and dried. It weighed 1.82 g. (92%); it showed no definite melting point, decomposing at about 285° to a brown tar.

3-Formyl-4,6-dimethyl-2-pyridone. A suspension of 30.0 g. of the benzenesulfonylhydrazide in 700 ml. of ethylene glycol was heated to 160° with stirring. Twenty-six g. of dry sodium carbonate was added all at once, keeping the temperature at 160–165°. The solution turned orange and a brisk effervescence took place. After 2–3 minutes the evolution of gas had ceased; water was added cautiously until the temperature had fallen to 120° and then enough more to make a total volume of two liters. The filtered solution was extracted thoroughly with chloroform. Evaporation of the chloroform left a red-brown crystalline solid which was recrystallized from water (charcoal) to yield 8.0 g. (56%) of the desired aldehyde as bright yellow prisms, m.p. 210° (dec.).

Anal. Calc'd for $C_8H_9NO_2$: C, 63.6; H, 6.00.
Found: C, 63.7; H, 6.2.

The compound readily formed a brick-red 2,4-dinitrophenylhydrazone, a yellow phenylhydrazine and a colorless semicarbazone. None of these was characterized.

Ethyl 2-methyl-4-hydroxypyrimidine-5-carboxylate was prepared in improved yield by modifying the procedure of Todd and Bergel (15).

A solution of 7.6 g. of sodium in 250 ml. of absolute alcohol was cooled to 0° and to it was added with stirring 31.0 g. of acetamidine hydrochloride. After a few minutes 71 g. of ethyl ethoxymethylenemalonate (16) was added and stirring was continued at 0° for three hours. A cooled solution of 7.6 g. of sodium in 250 ml. of alcohol was added and the solution was allowed to come to room temperature slowly and to stand overnight. The alcohol was removed by distillation (finally under reduced pressure) and the pale yellow, solid residue was dissolved in water. The solution was filtered, extracted with ether (ether discarded) and acidified with about 20 ml. of glacial acetic acid. Extraction of the aqueous solution with chloroform yielded 47.7 g. (86%) of the ester, which forms soft, white needles from acetone, m.p. 190.5–191.5° [reported (15), 191°].

2-Methyl-4-hydroxpyrimidine-5-carboxyhydrazide. A mixture of 15.0 g. of the ester, 70 ml. of water, and 10 ml. of 85% hydrazine hydrate was boiled under reflux for two hours. The cooled solution was acidified with acetic acid, cooled in ice, and the crystalline product ollected. There was obtained 10.3 g. (83%) of shining yellow leaflets. A sample recrystallized from water melted with decomposition at 242–243°.

Anal. Calc'd for $C_6H_8N_4O_2$: C, 42.8; H, 4.8.
Found: C, 42.7; H, 5.0.

The hydrazide readily formed a crystalline benzal derivative when treated with benzaldehyde in aqueous solution.

Benzenesulfonyl 2-methyl-4-hydroxypyrimidine-5-carboxhydrazide. To a suspension of 27.0 g. of the hydrazide in 100 ml. of warm pyridine was added slowly and with stirring, 30 g. of benzenesulfonyl chloride. The solution was poured onto ice and the solid collected and recrystallized from acetic acid. There was obtaned 41.4 g. of nearly colorless material (84%). The compound had no definite m.p., decomposing on heating.

Anal. Calc'd for $C_{12}H_{12}N_4O_4S$: C, 46.7; H, 3.9.
Found: C, 46.7; H, 4.2.

Attempt to prepare 2-methyl-4-hydroxypyrimidine-5-aldehyde. To a solution of 4.0 g. of the benzenesulfonyl hydrazide in 50 ml. of ethylene glycol, heated to 155°, was added, all at once, 3.0 g. of dry sodium carbonate. After the brisk effervescence had subsided (about 3 min.) the solution was cautiously diluted with water to 200 ml., cooled, and acidified with 3.5 ml. of glacial acetic acid. A crystalline precipitate of the benzenesulfonyl hydrazide separated; this was removed, and attempts made to isolate the aldehyde from the orange filtrate. No aldehyde could be obtained; its presence at least in small amount in the solution was indicated by the formation of a red precipitate when dinitrophenylhydrazine reagent was added to a portion of the solution. A repetition of the experiment led to no better result.

Substituted 3-formyl-4-hydroxyquinaldines. These were prepared by the Reimer-Tiemann formylation of the correspondng 4-hydroxyquinaldines according to the procedure employed by Conrad and Limpach (5). The hydroxyquinaldines were prepared by cyclizing the appropriate methyl N-substituted-β-aminocrotonates by the method of Limpach (17).

3-Formyl-4-hydroxyquinaldine, previously described by Conrad and Limpach (5), was obtained in 58% yield, m.p. 278–280° (dec.) [reported, 273° (dec.)]

4-Hydroxy-6-methylquinaldine was prepared by the addition of 20 g. of methyl β-*p*-toluidinocrotonate to 100 ml. of white paraffin oil (Standard Oil Co., No. 7) heated to 255–260°. The solution was stirred for 20 minutes (crystallization of the product began after 5 min.), cooled, diluted with petroleum ether, and filtered. The product (13 g., 70%) melted at 280–282° (dec.). [Reported (5), 274–275°.]

Anal. Calc'd for $C_{11}H_{11}NO$: C, 76.3; H, 6.4.
Found: C, 76.1; H, 6.3.

3-Formyl-4-hydroxy-6-methylquinaldine. A mixture of 13.5 g. of 4-hydroxy-6-methylquinaldine, 10 g. of sodium hydroxide, 100 ml. of 80% ethanol, and 30 ml. of chloroform was refluxed, with stirring, for two days. The salt was removed by filtration and the filtrate acidified with dilute acetic acid. The product (5.0 g., 35%) was crystallized from glacial acetic acid, forming orange needles, m.p. 300° (dec.).

Anal. Calc'd for $C_{12}H_{11}NO_2$: C, 71.7; H, 5.5.
Found: C, 71.4; H, 5.5.

The compound gave an orange-red crystalline 2,4-dinitrophenylhydrazone almost insoluble in boiling glacial acetic acid.

3-Formyl-4-hydroxy-7,8-benzoquinaldine. The 4-hydroxy-7,8-benzoquinaldine prepared, as described above for the 6-methyl derivative, from methyl β-(α-naphthylamino)crotonate, was formylated by refluxing 48 g. of it for 24 hours in a mixture of 50 g. of sodium hydroxide, 500 ml. of 90% ethanol, and 125 ml. of chloroform. After the recovery of 30 g. of starting material there was obtained 8.0 g. of the aldehyde which formed tan-yellow needles from glacial acetic acid, m.p. 308° (dec.).

Anal. Calc'd for $C_{15}H_{11}NO_2$: C, 76.0; H, 4.7.
Found: C, 75.8; H 4.8.

4-Hydroxy-6-bromo- and -8-chloro-quinaldines were formylated in the same way, but gave unsatisfactory yields of products difficult to purify. Both products gave the characteristic orange-red, insoluble (in hot glacial acetic acid) 2,4-dinitrophenylhydrazones, but work on

these substances was discontinued before the aldehydes were fully purified and characterized.

The Reimer-Tiemann reaction with 4-hydroxypyridine and 2,6-dimethyl-4-hydroxypyrimidine. Treatment of 4-hydroxypyridine (18) with sodium hydroxide and chloroform failed to yield the desired aldehyde. Some starting material and small amounts of oily materials were isolated.

Treatment of 5.0 g. of 2,6-dimethyl-4-hydroxypyrimidine with 20 g. of sodium hydroxide in 25 ml. of water and 12 g. of chloroform on the steam-bath for four hours, followed by neutralization and extraction with chloroform resulted in the recovery of starting material only.

o-Methoxyphenyllithium was prepared according to the directions of Gilman, Zoellner, and Selby (19).

2-o-Methoxyphenyl-1,2-dihydroquinoline. To an ether solution of *o*-methoxyphenyllithium prepared from 18.9 g. of *o*-bromoanisole and 1.4 g. of lithium was added, dropwise and with stirring, a solution of 12.9 g. of redistilled quinoline in 30 ml. of ether. The ether boiled and a yellow solid separated. After 15 minutes' stirring, water was added cautiously and the mixture stirred for an hour at 0°. After separation of the ether layer and drying it over sodium sulfate the solvent was evaporated. The residual orange syrup crystallized on scratching. The yield was 16 g. (68% based on the lithium used). After recrystallization from aqueous ethanol it melted at 86–88°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.1; H, 6.4.
Found: C, 80.9; H, 6.4.

The compound liquefied on standing, partially after one month, completely after four.

2-o-Hydroxyphenylquinoline. A solution of 15 g. of the dihydro compound in 50 ml. of nitrobenzene was refluxed for an hour and poured into dilute hydrochloric acid. The product, isolated from the acid solution, was distilled as a viscous yellow oil, b.p. 196°/2 mm., and without further treatment refluxed for 24 hours with a solution of 25 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid. The resulting solution was neutralized with sodium carbonate yielding a yellow solid, m.p., after crystallization from 80% alcohol as yellow needles, 114–115.5°. The yield of purified product was 6.0 g. Döbner (20) reports yellow needles, m.p. 115°.

1-o-Hydroxyphenylisoquinoline. To the organolithium compound prepared from 21.8 g. of *o*-bromoanisole and 1.6 g. of lithium was added 15 g. of isoquinoline. Isolation, oxidation, and demethylation of the product were carried out as described above without extensive purification or examination of the intermediate compounds. The yield of purified 1-*o*-hydroxyphenylisoquinoline, obtained as colorless prisms from ethanol, was 5.8 g.; m.p. 167–168°.

Anal. Calc'd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0.
Found: C, 81.1; H, 5.2.

The *picrate* formed clusters of yellow needles, m.p. 182–183° (after apparent dehydration at 100–105°).

Anal. Calc'd for $C_{21}H_{14}N_4O_8$: C, 56.0; H, 3.1.
Found: C, 55.9; H, 3.2.

2-o-Hydroxyphenylpyridine. By the same procedure, from 21.8 g. of *o*-bromoanisole and 15 g. of pyridine, was obtained 2.0 g. of *o*-hydroxyphenylpyridine. Much resinous material was obtained in the first step. The final product was a liquid, b.p. 135–145°/2 mm., which could not be crystallized. It was converted to its yellow picrate (m.p. 176–178°, with previous sintering) for analysis:

Anal. Calc'd for $C_{17}H_{12}N_4O_8$: C, 51.0; H, 3.0.
Found: C, 50.7; H, 3.2.

2,2'-Dipyridine. A modification of the method of Wilbaut and Overhoff (21) was used.

A suspension of 21 g. of copper powder in 200 ml. of cymene was stirred at 175–180° while 104 g. of 2-bromopyridine was added dropwise over one hour. Two additional portions of 21 g. each of copper powder were added during the addition of the bromopyridine. After heating for a further 2.5 hours the mixture was cooled and acidified with dilute HCl and

the cymene removed by steam distillation. The residual solution was made strongly basic and the dipyridine collected by steam distillation. The distillate was saturated with salt and extracted continuously with ether. Removal of the ether and distillation of the residue yeilded 31.5 g. of 2,2'-dipyridine, b.p. 147°/16 mm.

6,6'-Diphenyl-2,2'-dipyridine. This was prepared as a trial run before the use of *o*-methoxyphenyllithium was attempted.

An ether solution of phenyllithium prepared from 7 g. of bromobenzene and 0.56 g. of lithium was treated with a solution of 3.0 g. of 2,2'-dipyridine in 50 ml. of benzene. The solution became deep red and a red precipitate appeared. The ether was removed by distillation and the residual benzene solution refluxed for four hours with stirring. Water was added and after separation of the orange benzene solution, the latter was added to 5 ml. of nitrobenzene. This solution was heated on the steam-bath for a few minutes, when it became deep red in color. The volatile material was removed with steam and from the last portions of the steam distillate colorless crystals separated. This material (0.5 g.) was recrystallized from cellosolve, from which it formed colorless flakes, m.p. 176–178°. It gave no color with ferrous iron.

Anal. Calc'd for $C_{22}H_{16}N_2$: C, 85.7; H, 5.2.
Found: C, 85.4; H, 5.4.

6,6'-Bis-(o-methoxyphenyl)-2,2'-dipyridine. To an ice-cold ether solution of *o*-methoxyphenyllithium, prepared from 16.5 g. of *o*-bromoanisole and 1.1 g. of lithium, was added very slowly and with vigorous stirring a solution of 6.5 g. of 2,2'-dipyridine in 100 ml. of ether. The resulting brown solution was stirred overnight at 0°, after which ice and 10 ml. of nitrobenzene were added. The ether layer was separated, the ether evaporated and the residue distilled. The portion boiling at 130–250°/3 mm. was collected and redistilled, after which there was obtained 5.3 g., b.p. 190–195°/2 mm. No attempt was made to purify this further, a dipicrate being prepared for analysis; it formed fine yellow needles (from cellosolve), m.p. 211–212°.

Anal. Calc'd for $C_{36}H_{26}N_8O_{16}$: OCH_3, 7.51. Found: OCH_3, 7.39.

6,6'-Bis-(o-hydroxyphenyl)-2,2'-dipyridine. A solution of 14.0 g. of the methoxy compound in 250 ml. of 48% hydrobromic acid was refluxed overnight, poured onto ice, and neutralized with sodium carbonate. The amorphous solid was separated and crystallized from methanol. The pure compound (6.8 g.) formed clusters of yellow needles, m.p. 102.5–103.5°.

Anal. Calc'd for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7.
Found: C, 77.5; H, 4.9.

The *dipicrate*, recrystallized from cellosolve, formed a yellow powder, m.p. 193.5–195°.

Anal. Calc'd for $C_{34}H_{22}N_8O_{16}$: C, 51.1; H, 2.8.
Found: C, 51.1; H, 2.9.

Experiments on dehydrogenation of 2-phenyl-1,2-dihydropyridine derivatives. A. The product (25% yield) from the reaction of phenyllithium with pyridine in ether (carried out at the boiling point of ether) was a yellow oil; this formed a picrate, m.p. 172–174°, with the formation of an intense red coloration in the course of the reaction with picric acid.

B. When the hydrolysis of the pyridine-phenyllithium reaction mixture was followed by the immediate addition of nitrobenzene and completion of the dehydrogenation by a short period of heating on the steam-bath, a 60% yield of 2-phenylpyridine, b.p. 100–105°/2 mm., was obtained. This formed a picrate identical with that described in A, but during its formation, no unusual color appeared in the reaction mixture.

C. The reaction of phenyllithium with quinoline in ether (at room temperature) produced first a brown color and, after 15 minutes, a yellow precipitate. Hydrolysis, separation of the ether layer, and distillation of the product yielded a yellow oil (45% yield), b.p. 175–185°/4 mm. The picrate formed with the appearance of an intense red color in the solution; m.p. 188–190° (orange plates from cellosolve).

D. After the addition of quinoline to phenyllithium and hydrolysis of the reaction mixture, the ether layer was separated, added to 25 ml. of nitrobenzene, and warmed on the

steam-cone until the ether had evaporated. The product (78% yield) obtained by removal of the nitrobenzene and distillation, crystallized immediately. It formed clusters of yellow needles from methanol, m.p. 78–81°. The picrate formed without the appearance of the red coloration described in B; m.p. 190–191°. It showed no depression on mixing with the picrate described under B.

SUMMARY

A number of new compounds have been prepared for use in studies on metal chelates similar to salicylaldehyde ethylenediimine cobalt ("Salcomine"). Among these have been (a) aromatic and heterocyclic *o*-hydroxyaldehydes intended to replace salicylaldehyde, and (b) derivatives of 2-*o*-hydroxyphenylpyridine, intended to fill the role of salicylaldehyde ethylenediimine, in such complexes.

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REFERENCES

(1) Shoesmith and Haldane, *J. Chem. Soc.*, 2704 (1923).
(2) Tiemann and Lewy, *Ber.*, **10**, 2211 (1877).
(3) Russell and Frye, *Org. Syntheses*, **21**, 23 (1941).
(4) Russell, Frye, and Mauldin, *J. Am. Chem. Soc.*, **62**, 1441 (1940).
(5) Conrad and Limpach, *Ber.*, **21**, 1972 (1888).
(6) MacFayden and Stevens, *J. Chem. Soc.*, 584 (1936).
(7) Niemann and Hays, *J. Am. Chem. Soc.*, **65**, 482 (1943).
(8) Bergmann, Blum-Bergmann, and v. Christiani, *Ann.*, **483**, 80 (1930).
(9) Ziegler and Zeiser, *Ann.* **485**, 174 (1931).
(10) Robinson and Shah, *J. Chem. Soc.*, 1491 (1934).
(11) Helferich, *J. prakt. Chem.*, **151**, 252 (1938).
(12) Bardham, *J. Chem. Soc.*, 2223 (1929).
(13) Simonsen and Naik, *J. Chem. Soc.*, **107**, 793 (1915).
(14) Moir, *J. Chem. Soc.*, **81**, 115 (1904).
(15) Todd and Bergel, *J. Chem. Soc.*, 357, 364 (1937).
(16) Claisen, *Ann.*, **297**, 76 (1897).
(17) Limpach, *Ber.*, **64**, 969 (1931).
(18) Koenigs and Greiner, *Ber.*, **64**, 1069 (1931).
(19) Gilman, Zoellner, and Selby, *J. Am. Chem. Soc.*, **55**, 1252 (1933).
(20) Döbner, *Ann.*, **249**, 101 (1888).
(21) Wilbaut and Overhoff, *Rec. trav. chim.*, **47**, 761 (1928).