The Synthesis of 5-Oxoperhydroisoquinolines

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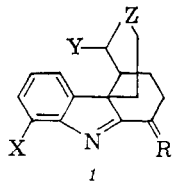
The syntheses of 2-acetyl-5-oxodecahydroisoquinoline (*18*), 1-carboxy-2-acetyl-5-oxodecahydroisoquinoline (*2*), and 2-acetyl-5,6-dioxodecahydroisoquinoline-6-ethylenedithioketal (*24*) are described. The Henze–Reissert reaction was conducted on 5-hydroxyisoquinoline N-oxide. Some experiences in attempted C-alkylation of dihydroresorcinol are described.

The initial observation that arylhydrazones of α-decalone and 5-oxodecahydroisoquinoline could be caused to rearrange to tetrahydrocarbazolenines (*1*)[2], grossly similar to the morphinoid class of



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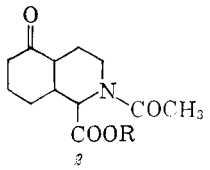

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substances, prompted an investigation into the synthesis of the appositely substituted perhydroisoquinoline derivative *2* necesary to the preparation of *1* (R = H_2, X = OCH_3, Y = COOH, Z = $NCOCH_3$ or $N—CH_3$,) functionalized suitably for the phenanthrenoid ring closure at an appropriate step in a contemplated synthesis of morphine and/or analogous substances. We wish to report herein the synthesis of 1-carboxy-2-acetyl-5-oxodecahydroisoquinoline (*2*) as well as 2-acetyl-5-oxodecahydroisoquinoline. The study of the carbazolenine rearrangement of the arylhydrazones of these heterocyclic ketones and of other model alicyclic ketones will be the subject of a separate communication.

An attractive route to the general structure embodied in *2* was initially considered as one stemming from dihydroresorcinol and is outlined in Figure 1. In principle the routes portrayed in Figure 1 could lead to the cyclic amides shown or to the extracyclic amide *2*. Since it was necessary for the projected carbazolenine rearrangement to *1* to have the perhydroisoquinoline nitrogen incorporated as a neutral, or nearly neutral, function, it was felt that it might be of interest to have available for the purposes of this rearrangement both classes of of amides. This first approach to variously functionalized 5-oxoperhydroisoquinolines was investigated, and while some interesting results were obtained, the method was generally unrewarding.

Dihydroresorcinol (*3*), subject to both carbon and oxygen alkylation, has been studied extensively by Stetter[3] in the matter of influencing the balance between these alternative modes of alkylation. Thus under conditions ascertained as optimal for C-alkylation in the production of carboethoxymethylcyclohexanedione (*4*),[3] dihydrohydroresorcinol was treated with potassium ethylate and ethyl *N*-chloroacetylsarcosinate (*7*) (or the corresponding iodoacetyl compound generated *in situ*), in the hope of obtaining *8* with structure *9* as the ultimate goal. The major course of reaction, however, was that resulting from O-alkylation,[4] compound *10*. The only C-alkylation product proved to be, peculiarly, the cyclohexanedione–acetic ester *4*. It is difficult to say whether substance *4* is generated from initially formed *8* followed by intermolecular amide cleavage by ethoxide ion or intramolecular attack of enolate oxygen on amide carbonyl with expulsion of sarcosine ester generating *11*, which could then suffer ethoxide cleavage to yield the enolate of *4*. Though appreciable concentrations of the enol–lactone *11* would not be expected in the equilibria involved, its production by an intramolecular process could supply it as a reactive intermediate.

Since it was evident that the direct introduction of the entire preformed set of atoms required in the heterocyclic portion of the hydroisoquinoline system could not be accomplished on carbon, it was next decided to investigate the use of substance *4*, already bearing correctly situated one terminus of the nitrogen ring. Substance *4* was converted with phosphorus trichloride to the chlorocyclohexenone *5*, an analogous conversion already having been reported in the case of the simpler 3-chlorocyclohex-2-en-1-one.[5] As the latter had been used to alkylate malonic and substituted malonic esters,[6] it was hoped to effect appendage of the N—C—COOR chain incorporated in acetamidomalonic ester at C-3 of *5* with structure *12* as the synthetic target by this route. This alkylation, however, did not prove successful, since acetamidomalonic ester was largely recovered from the reaction. A similar result was encountered in the attempted

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(2) V. Georgian, *Chem. Ind.* (London), 1124 (1957).

(3) H. Stetter and W. Dierichs, *Ber.*, **85**, 61, 290 (1952).

(4) For a discussion of the alkylation of ambident anions, see: N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(5) A. W. Crossley and P. Haas, *J. Chem. Soc.*, **83**, 498 (1903).

(6) G. R. Clemo, W. Cocker, and S. Hornsby, *ibid.*, 616 (1946). A. W. Crossley and C. Gilling, *ibid.*, **95**, 24 (1909).

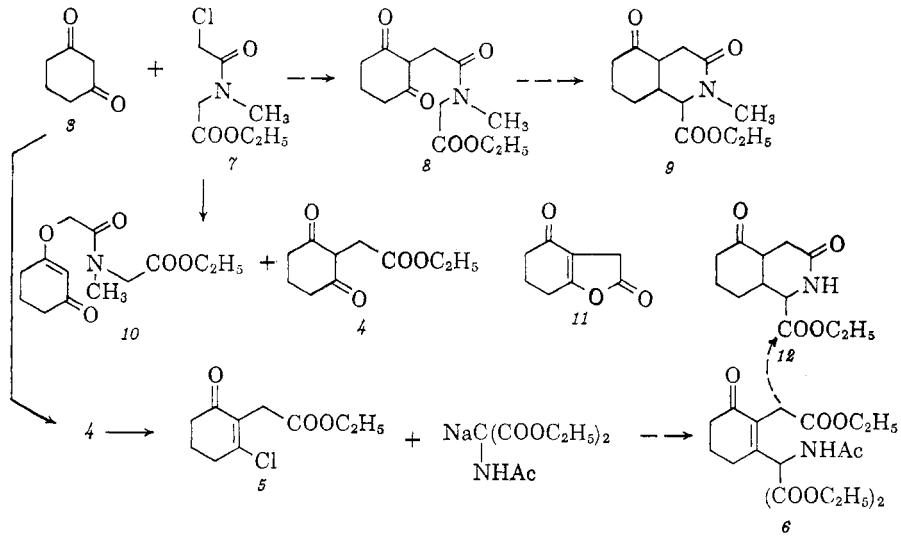


Figure 1

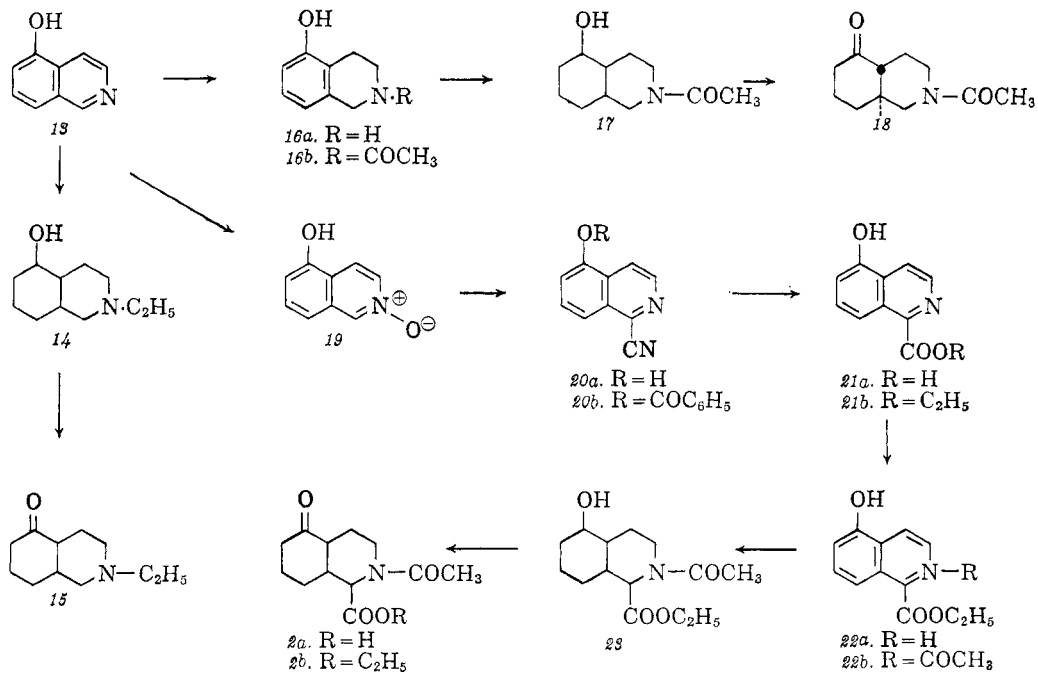


Figure 2

alkylation of acetamidomalonic ester with 3-chlorocyclohexenone, and so this approach was abandoned.

Inasmuch as a direct synthesis of the hydroisoquinoline system bearing a 5-carbonyl and a 1-carboxyl function did not appear very feasible or efficient by the methods contemplated above, attention was next turned to the transformation of isoquinoline itself. This ring system may be cationically substituted predominately at C-5[7] and is further amenable to introduction of carboxyl at C-1 by the Reissert reaction[8] sequence.

The problem of the synthesis of the simpler 5-oxodecahydroisoquinoline was approached first, as methods worked out for it could be applied to the 1-carboxy analogue. 5-Hydroxyisoquinoline, which is also preparable by the acid hydrolysis of 5-aminoisoquinoline, was more conveniently available by the alkaline fusion[9] of isoquinoline-5-sulfonic acid.[10] It was exposed to high pressure catalytic hydrogenation over W-7 Raney nickel in absolute ethanol with a trace of alkali, conditions gauged to minimize hydrogenolysis of the

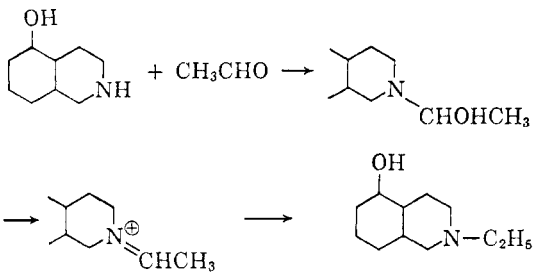
(7) Refer to R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.*, **67**, 860 (1945), footnotes 24 and 25, for a summary discussion and correlation of orientation in aromatic substitution in isoquinoline.

(8) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(9) A modification of the methods of C. F. Koelsch and N. F. Alberts, *J. Am. Chem. Soc.*, **75**, 2095 (1953) and of R. A. Robinson, *ibid.*, **69**, 1943 (1947).

(10) L. F. Fieser and E. L. Martin, *ibid.*, **57**, 1843 (1935).

oxygen function[11] in the cases of naphthols and phenols. The product initially considered to be the decahydro derivative, was shown, on elemental analysis of its picrate and oxidation to a nonacetylatable ketone *15*, to be in fact N-ethyl-5-hydroxydecahydroisoquinoline (*14*). The generation of this tertiary amine may be explained by postulating catalytic dehydrogenation of ethanol to acetaldehyde and reductive combination of the latter with the reduced isoquinoline through a carbinolamine, a scheme for which there is some precedent[12]:



It was thus necessary to effect the over-all ring hydrogenation in two stages with acetylation of the nitrogen interposed between the two reductions. The heterocyclic reduction to the tetrahydro stage *16a* was accomplished over platinum, and hydrogenation to the decahydro stage *17* was now satisfactorily accomplished on *16b* under the nonhydrogenolytic conditions mentioned above. Oxidation afforded the desired 2-acetyl-5-oxodecahydroisoquinoline (*18*). Though no definite corroborative proof of the stereochemistry is available for this ketone, only one isomer appears to have been formed from the conversion to a homogeneous dinitrophenylhydrazone derivative. From the synthetic route employed—*i.e.* one involving hot high pressure nickel hydrogenation and chromic acid oxidation in the presence of sulfuric acid—the ketone *18* is most likely the *trans* isomer.[13]

An analogous scheme was to be applied to 5-hydroxyisoquinaldic acid (ester) (*21a,b*), but awaited a satisfactory synthesis of the latter. Isoquinaldic acid[14] was nitrated,[15] and the position of nitration was established by decarboxylation of the nitroisoquinaldic acid over copper chromite.

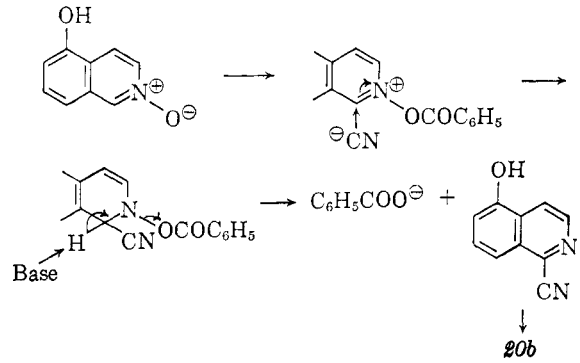


Figure 3

The resulting 5-nitroisoquinoline indicated functionalization of the proper position on the nucleus, but subsequent transformations such as reduction to 5-aminoisoquinaldic acid or ester and attempted replacement of the 5-amino group with hydroxyl did not proceed as satisfactorily as desired.

Attention was thus directed toward the introduction of the carboxyl function into 5-hydroxyisoquinoline. Although the Reissert reaction sequence came to mind, it was felt that in principle the rather vigorous treatment necessary in the elimination of the elements of benzaldehyde from Reissert compounds detracted considerably from the application of this method to 5-hydroxyisoquinoline. Benzaldehyde certainly cannot be considered as a good leaving group even though aromatization ensues. And so the amine oxide variant of this reaction[16] was considered. In this reaction scheme the heterocyclic base is first converted to the amine oxide, and this is then treated with an aqueous cyanide solution and benzoyl chloride. The mechanistic sequence may be considered as that portrayed in Figure 3, from which it may be seen that the benzoyl moiety, having coördinated with the oxide, is now permitted facile departure as benzoate. The formation of the latter, together with the resulting aromatization of the heterocyclic ring, must contribute deriving force to the reaction. Possibly because of this, the Henze–Reissert compound, 1-cyano-N-benzoxydihydroisoquinoline derivative, is not isolable, as is the case with the usual Reissert derivatives. Since it has been shown that no cyanoquinoline is formed from quinoline N-oxide without the intervention of benzoyl chloride, the inference may be drawn that prior coördination of benzoyl with oxide is necessary to increase the acceptor character of the adjacent carbon.[17] The experimental observation in the

(11) H. E. Unguade and A. D. McLaren, *J. Am. Chem. Soc.*, **66**, 118 (1944); H. E. Unguade and D. V. Nightingale, *ibid.*, **66**, 1218 (1944); W. S. Johnson, C. D. Gutsche, and D. K. Banerjee, *ibid.*, **73**, 5464 (1951).

(12) For additional examples of alkylation of amines with alcohols in the presence of Raney nickel, see C. Winans and H. Adkins, *ibid.*, **54**, 306 (1932); K. H. Shah, B. D. Tilak, and K. Venkataraman, *Proc. Ind. Acad. Sci.*, **28A**, 145 (1948); E. C. Kornfeld, *J. Org. Chem.*, **16**, 131 (1951); R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955); C. Ainsworth, *ibid.*, **78**, 1635 (1956); K. Venkataraman, *J. Ind. Chem. Soc.*, **35**, 1 (1958).

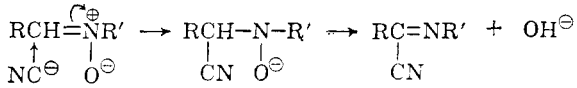
(13) Under such conditions *trans*-α-decalone results from α-naphthol.

(14) W. Solomon, *J. Chem. Soc.*, 129 (1947), and J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945), have shown that the Reissert compound of isoquinoline is best cleaved with 65% sulfuric acid, the generated benzaldehyde then being steam distilled.

(15) Using the method of C. G. LeFevre and R. J. W. LeFevre, *J. Chem. Soc.*, **137**, 1470 (1935).

(16) M. Henze, *Ber.*, **69**, 1566 (1936).

(17) It is interesting to note that in the Bellavita reaction [V. Bellavita, *Gazz. chim. ital.*, **65**, 889, 897 (1935); F. Kröhnke, *Ann.*, **604**, 203 (1957)], which is the acyclic analogue of the Henze–Reissert reaction, no acylating agent is required in the conversion of a nitrone by means of cyanide to an α-ketiminonitrile:



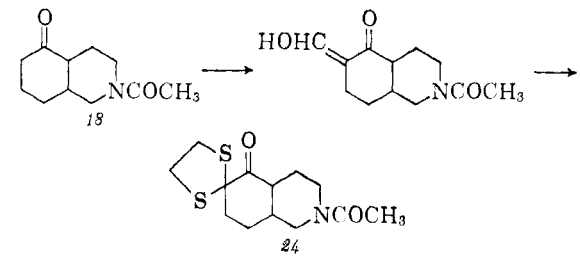


Figure 4

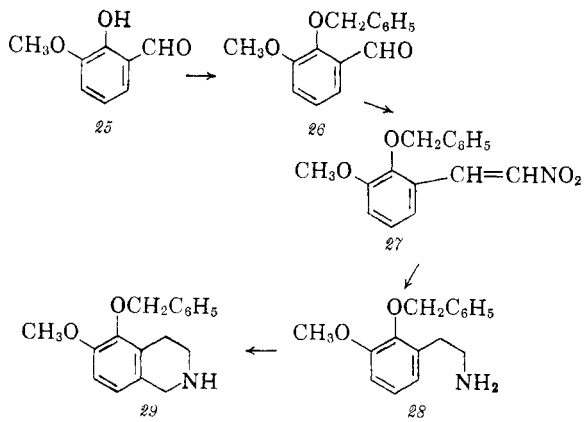


Figure 5

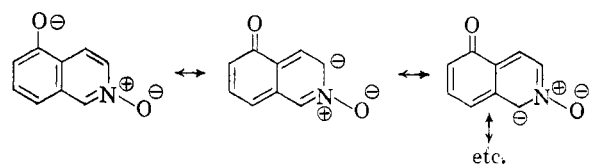
reaction with 5-hydroxyisoquinoline N-oxide (*19*) was that complete solution of the latter resulted in the aqueous potassium cyanide, and slow introduction of benzoyl chloride precipitated the product *20b*. The initial solution of *19* may have resulted from interaction of cyanide ion with the N-oxide at C-1, prior to benzoxy formation, or from solution of the rather strongly acidic phenolic group encountered in the system of *19* (*vide infra*). In any case, the Henze–Reissert reaction is extremely facile and would appear to be the method of choice over the usual procedure, especially with sensitive systems, although it has been reported in relatively few instances on quinolines[18] and only once on an isoquinolines.[19]

An interesting observation was made on 5-hydroxyisoquinoline N-oxide (*19*) that it was a much stronger acid than 5-hydroxyisoquinoline or ordinary phenols. It was found in fact to be soluble in dilute bicarbonate solution, by which means it could be separated from any 5-hydroxyisoquinoline. Inspection of some of the canonical resonance forms for delocalizing the phenolate ionic charge will reveal that direct resonance involvement of the positive nitrogen is by-passed, and cannot be invoked as explanation. (see col. 2). The acid strengthening effect may therefore be accounted for on a π-inductive basis or more likely by the less circuitous route of a direct field effect.[20]

The remainder of the route from the benzoxy-nitrile (*20b*) to *2a,b* was as shown in Figure 2. Alkaline hydrolysis to *21a*, esterification to *21b*, platinum reduction (*22a*), acetylation in methanolic solution to avoid O-acetylation (*22b*), nickel reduction as with *16b* → *17* to yield *23*, and oxidation[21] afforded the desired 1-carboxy (or carbethoxy)-2-acetyl-5-oxodecahydroisoquinoline (*2a,b*).

For some applications held in mind for the rearrangement studies on the arylhydrazones of the heterocyclic ketones reported above it was considered desirable to have included at C-6, alpha to the carbonyl group at C-5, an additional oxygen function in the form of alkoxyl or masked keto group. The latter could serve as a blocking group directing hydrazone rearrangement toward the bridgehead carbon as well as providing a carbonyl function at this carbon atom in the resulting tetrahydrocarbazolenine *1* (R=O).[22] Since a dithioketal function could be incorporated directly on the methylene carbon alpha to the 5-keto group,[23] ketone *18* was transformed according to the scheme set forth in Figure 4. Ketone *18* was formylated in the usual manner and the hydroxymethylene derivative was then treated with ethylenebis-toluenethiosulfonate to yield 2-acetyl-5,6-dioxodecahydroisoquinoline 6-ethylenedithioketal (*24*).

To make available differentially protected 5,6-dioxygenated hydroisoquinolines potentially transformable to 6-alkoxy-5-oxoperhydroisoquinolines, 5-benzyloxy-6-methoxytetrahydroisoquinoline was synthesized starting from *o*-vanillin (*25*)[24] as pictured in Figure 5 *via* the Pictet–Spengler[25] route. Attempts to condense the benzyloxymethoxyphenethylamine (*28*) with ethyl glyoxylate did not yield



(18) E. Ochiai and I. Nakayama, *J. Pharm. Soc. Jap.*, **65**, No. 9/10A, 7 (1945). I. Nakayama, *ibid.*, **70**, 355, 423 (1950). F. Montanari and L. Pentimalli, *Gazz. chim. ital.*, **83**, 273 (1953). M. Colonna and S. Fatutta, *ibid.*, **83**, 622 (1953).

(19) E. Ochiai and Z.-R. Sai, *J. Pharm. Soc. Jap.*, **65**, No. 4A, 17 (1945).

(20) For analogous field effects on ultraviolet absorption, or base strengths of amines, see V. Georgian, *Chem. Ind.* (London), 930 (1954); *ibid.*, 1480 (1957); C. A. Grob, A. Kaiser, and E. Renk, *ibid.*, 598 (1957); 1222 (1955). See also J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953), for field effects on acid ionization.

(21) Using either (a) chromic acid–pyridine method[37] or (b) chromic acid–acetone method: A. Bowers, T. J. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(22) This aspect of our work will be presented in a forthcoming publication of this series.

(23) For the transformation  see R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(24) Monsanto Chemical Company, St. Louis, Mo.

(25) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, John Wiley & Sons, Inc., New York, N. Y., 1900, p. 151.

a recognizable product, as was also the case with ethylglyoxylate and homoveratrylamine.

Experimental[26]

Ethyl Sarcosinate.[27]—Methylamine hydrochloride (270 g.) was treated with 500 ml. of 40% formaldehyde solution and 260 g. of potassium cyanide. Work-up in the usual manner yielded 264 g. (88%) of sarcosinenitrile, which was then esterified with dry hydrogen chloride in 95% ethanol (2 l.) to yield ethyl sarcosinate; b.p. 58–61° (25 mm), $n^{25}D$ 1.4167.

Ethyl N-Chloroacetylsarcosinate.—Sarcosine ethyl ester (110 g.) in 1 l. of ether was stirred vigorously with 85% anhydrous potassium carbonate in 75 ml. of water. To the mixture was added 120 g. of freshly distilled chloroacetyl chloride in 500 ml. of ether at such a rate that the ether refluxed gently (*ca.* 1.5–2 hr.). After the addition was complete, more potassium carbonate was added until the lower layer consisted of a paste. The ether layer was then decanted and the paste was washed several times with fresh ether. Evaporation of the dried ($MgSO_4$) ether extract ion and distillation afforded the product, 150 g. (83%), b.p. 140° (3 mm.). Infrared showed ester carbonyl (5.77 μ) and amide carbonyl (6.03 μ).

Reaction of Dihydroresorcinol and Ethyl N-chloroacetylsarcosinate.—To a solution of 1.2 g. of potassium in 50 ml. of anhydrous ethanol there was added 3.0 g. of dihyroresorcinol[28] and 1 g. of potassium iodide. After several minutes 6 g. of ethyl N-chloroacetylsarcosinate was added and the mixture was refluxed with stirring for 5 hr. (until reaction neutral to litmus). The solution was diluted with water and the product was extracted with chloroform. The chloroform extract was washed with cold 3 *N* sodium hydroxide. Evaporation of the washed and dried chloroform solution gave 3.1 g. of neutral material which gave a negative ferric chloride test, was probable O-alkylation product (*10*), and was not further investigated.

Acidification of the sodium hydroxide solution gave a water soluble product which was extracted into chloroform. Evaporation of this solution produced a solid (1.2 g.) which showed a purple ferric chloride coloration. Recrystallization from water (Norite) gave m.p. 93.5–94.5°. Drying *in vacuo* at 50° gave a m.p. 80–81°, and recrystallization from water raised the m.p. to the former value. This is the behavior of Stetter's ethyl cyclohexanedioneacetate (*4*) which forms a hydrate; mixed m.p. with authentic *4* as hydrate showed no depression.

Attempts to effect alkylation of the dihydroresorcinol *via* the pyrrolidine[29] eneamine[29] thereof [produced by azeotropic distillation of 13.5 g. of dihydroresorcinol and 34 g. of pyrrolidine in 500 ml. benzene; 17.5 g., b.p. 190–200° (0.1 mm.)] using ethyl chloroacetylsarcosinate and potasssium iodide in methanol resulted again in essentially only O-alkylated, alkali insoluble, product.

Alkylation of 2,4-dihydroresorcinol dimethyl ether[30] in liquid ammonia with potassium amide and ethyl chloroacetylsarcosinate was also unsuccessful as most of the diene was recovered and the product after aqueous acid treatment, b.p. 170–180° (0.25 mm.), had infrared absorption inconsistent with that expected for the product *8*.

Acetamidomalonic acid diethyl ester was prepared according to the method of M. Vignau.[31]

2-Carbethoxymethyl-3-chlorocyclohex-2-en-1-one.—2-Carbethoxymethyldihydroresorcinol hydrate (40.0 g.) was taken up in boiling benzene to eliminate the water of hydration by azeotropic distillation. Last traces of benzene were taken off *in vacuo* and the residue was dissolved in chloroform, dried over anhydrous magnesium sulfate, filtered, and the volume of the chloroform filtrate was adjusted to *ca.* 150 ml. Phosphorus trichloride (9.0 g.) was added and the reaction was refluxed 2 hr. The cooled reaction solution was decanted from separated phosphorous acid into a separatory funnel, ether being used in the transfer washings. The ether–chloroform solution was washed with cold water and extracted with cold 3 *N* sodium hydroxide solution until no more starting diketone was precipitated from the acidified alkaline extract. Approximately 2 g. of solid diketo ester was recovered in this way.

The organic solution was then washed with cold water to neutrality and with saturated sodium chloride solution and was dried over sodium sulfate. Distillation through a 12-in. Vigreux column afforded 28 g. of clear colorless slightly viscous oil, b.p. 144–145° (9–10 mm.), or 108° (0.1 mm.). Infrared showed no hydroxyl band, C=O bands at 5.80, 5.97 μ, and conjugated C=C at 6.14 μ.

Anal. Calcd. for $C_{10}H_{13}O_3Cl$: C, 55.44; H, 6.05. Found: C, 55.84; H, 5.76.

Attempted Condensation of Acetamidomalonic Ester and 2-Carbethoxymethyl-3-chlorocyclohex-2-en-1-one.—Acetamidomalonic ester (5 g.) was added to a solution of sodium (0.53 g.) in 20 ml. absolute ethanol, and to this solution after 10 min. was added 5 g. of 2-carbethoxymethyl-3-chlorocyclohex-2-en-1-one. The reaction was stirred and refluxed until it was neutral and the alcohol was removed *in vacuo*. The residual oil was taken up in ether and water (mainly water soluble). The aqueous layer was acidified slightly with acetic acid, saturated with ammonium sulfate, and extracted with ether. The combined ether solution was washed with 10% sodium carbonate, dried over potassium carbonate and sodium sulfate, and evaporated. A small quantity of acetomidomalonic ester, m.p. 92–93° separated, the residual oil was distilled, b.p. 120–130° (0.1–0.2 mm.). Infrared inspection showed this to be essentially recovered acetamidomalonic ester. Most of it crystallized and was washed with cyclohexane, m.p. 92–94°; mixed m.p. with acetamidomalonic ester gave no depression.

Isoquinoline-5-sulfonic Acid.—This preparation was carried out in a slight modification of that of Fieser and Martin.[10] Isoquinoline (52 g., 47.5 ml.) was added to 22 ml. conc. of sulfuric acid with ice cooling in a 500-ml. Erlenmeyer flask. With ice bath cooling and swirling 110 ml. of 50% fuming sulfuric acid was added and the clear solution was allowed to stand, with occasional swirling, at room temperature for 48 hr. It was then poured onto crushed ice (700 g.) and after standing overnight in the cold room the long white needles of sulfonic acid were filtered and pressed dry of mother liquor with a rubber dam. The filter cake was slurried with 50 ml. of water on the steam bath, cooled well in an ice bath, filtered, and washed with ice water (rubber dam). This material could be dried well in an oven at 70° overnight *in vacuo*. Yield 58 g. (70%).

5-Hydroxyisoquinoline (*13*). The following modification was found to be superior to the previous method of preparation.[9] Higher fusion temperatures and shorter reaction times gave a more controlled reaction.

A mixture of 420 g. of potassium hydroxide and 420 g. of sodium hydroxide was fused at 210° and 250 g. of powdered isoquinoline-5-sulfonic acid was added to the stirred melt at such a rate that the reaction was vigorous but not too violent. This addition required about 3–5 min. Without further heating the temperature rose to 260°, where it was maintained for 5 min., cooled quickly, and dissolved in 2.4 l. of

(26) All melting points are corrected. Infrared spectra were obtained on a Baird double beam spectrophotometer, Model AB-2. Microanalyses were performed by Miss Hilda Beck at the Microanalytical Laboratory, Department of Chemistry, Northwestern University. We are most grateful to Dr. Burris Tiffany, The Upjohn Company, Kalamazoo, Mich., for repeating many of the syntheses reported.

(27) W. Staudt, *Z. Physiol. Chem.*, **146**, 286 (1925).

(28) R. B. Thompson, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons Inc., New York, N. Y., 1955, p. 278.

(29) F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953); G. Stork, R. Terrell, and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

(30) A. J. Birch, *J. Chem. Soc.*, 102 (1947).

(31) M. Vignau, *Bull. Soc. chim. France*, 638 (1952).

water. The alkali was neutralized with acetic acid (880 ml.) and the cooled mixture was filtered. The product was taken up in 2 *N* hydrochloric acid, treated with Norite, and the filtered solution was neutralized with concentrated ammonia until just alkaline. Filtration of the cooled suspension yielded 157 g. (90%) of 5-hydroxyisoquinoline, m.p. 215–220° of sufficient purity for subsequent manipulations. *Picrate*, from ethanol, m.p. 255–257° (dec.)

Anal. Calcd. for $C_{15}H_{10}O_8N_4$: C, 48.2; H, 2.70. Found: C, 48.3; H, 2.75.

1,5-Dihydroxyisoquinoline is the principal product of prolonged fusion. Isoquinoline-5-sulfonic acid, 5 g., was fused with 10 g. each of potassium and sodium hydroxides at 230° for 0.5 hr. The melt (slightly cooled) was poured into 50 ml. of water, and 16 ml. of glacial acetic acid was added. The solid, filtered from the cooled precipitation, was recrystallized from 3 *N* hydrochloric acid–Cellosolve (Norite). Fine colorless needles were produced, m.p. 275–277° (lit.[32] 273°). That this substance, assigned the structure 1,5-isoquinolinediol,[9] is in fact an isocarbostyryl derivative was shown by the fact that it was readily convertible to a hydroxychloro derivative by the usual phosphorus oxychloride method (*vide infra*).

1-Chloro-5-hydroxyisoquinoline.—1,5-Dihydroxyisoquinoline (4 g.) was dissolved in 25 ml. of phosphorus oxychloride and heated in a sealed tube at 160° for 6 hr. On being cooled, the excess phosphorus oxychloride was taken off *in vacuo*, ice was added to the residue and then sodium hydroxide until short of neutrality, and the reaction mixture was then made neutral with sodium bicarbonate solution and the product filtered. It could be recrystallized with difficulty from aqueous alcohol whereafter it fails to melt but sinters at 200° with no further change apparent. If immersed in m.p. apparatus at 225–230°, it melts with decomposition.

Anal. Calcd. for C_9H_6ONCl: C, 60.18; H, 3.37. Found: C, 60.25, H, 3.36.

N-Ethyl-5-hydroxydecahydroisoquinoline (*14*).—5-Hydroxyisoquinoline (17.5 g.) in a solution of five sodium hydroxide pellets in 125 ml. absolute ethanol was hydrogenated over 4–5 g. of W-7 Raney nickel[33] at an initial hydrogen pressure of 3000 p.s.i. and at 125.0° No hydrogenation proceeded below this temperature. The theoretical uptake of hydrogen required *ca.* 4 hr. The product was a thick colorless oil, b.p. 100–105° (0.25–0.35 mm.); yield 17.2 g. (94%). The oil was characterized as the *picrate*, prepared and recrystallized from ethanol, m.p. 193–194°.

Anal. Calcd. for $C_{17}H_{24}O_8N_4$: C, 49.6; H, 5.87. Found: C, 49.5; H, 5.56.

N-Ethyl-5-oxodecahyroisoquinoline (*15*).—A cold solution of 5-hydroxydecahydroisoquinoline (4.0 g.) in 65 ml. of water was added to an ice-cold solution of 2.6 g. (1.5 equiv.) of chromic acid in 100 ml. of water and 8 ml. of conc. sulfuric acid. After 15 min. the reaction was allowed to come to room temperature at which it stood for 14 hr. Methanol (2 ml.) was added to destroy excess oxidizing power and after 2 hr. solid potassium carbonate was added until pH paper was deep blue. The slurry was extracted thoroughly with five 125-ml. portions of ether which were then dried over sodium sulfate. The product, N-ethyl-5-oxodecahydroisoquinoline (*15*) distilled as a clear straw colored oil, 2.4 g. (61%), oil bath at 156–161° (18 mm.) or 105–110° (0.2–0.3 mm.). It crystallized at ice temperatures and remelted at room temperature. Infrared showed no OH nor NH but C=O at 5.86 μ. It was recovered unchanged on attempted acetylation.

A yellow *picrate* formed from ethanol, m.p. 187–188°.

Anal. Calcd. for $C_{17}H_{22}O_8N_4$: C, 49.8; H, 5.41. Found: C, 49.7; H, 5.42.

2-Acetyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline (*16b*). Twenty nine grams of 5-hydroxyisoquinoline was dissolved in 200 ml. of glacial acetic acid with the aid of steam bath warming, and the solution was hydroge nated over 1.5 g. o Adams catalyst in a Parr apparatus at 35–40 p.s.i. In *ca.* 10 hr. two molecular equivalents of hydrogen was taken up. The solution, after filtration, was evaporated *in vacuo*, and the solid residue was taken up in 140 ml. of hot methanol and allowed to cool slightly.

Acetic anhydride (50 ml.) was added in portions during 15–20 min., and the reaction was allowed to stand at room temperature 0.5 hr. The volatile matter was removed *in vacuo* on the steam bath, the product was taken up in an equivalent amount dilute sodium hydroxide solution, treated with Norite, filtered, and the phenol was regenerated with dilute hydrochloric acid. After being well cooled for several hours, the product was filtered, 33 g. (87%). It could be recrystallized from acidulated water and then from dilute alcohol, m.p. 172–174°.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.1; H, 6.85. Found: C, 69.4; H, 7.12.

2-Acetyl-5-hydroxydecahydroisoquinoline (*17*).—2-Acetyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline (95.5 g.) was dissolved in 350 ml. of absolute alcohol, containing three sodium hydroxide pellets. It was shaken with 15–20 g. W-7 Raney nickel[33] and hydrogen at an initial pressure of 1600 p.s.i. Hydrogenation commenced when the temperature rose to 105–110° and was conducted at 120°, whereupon three molar equivalents of hydrogen were absorbed in 6 hr. The product, 82 g. (84%), was a water white glassy liquid, b.p. 163–166° (0.20–0.25 mm.), or 189–193° (2.0 mm.). Infrared spectra showed amide C=O at 6.12 μ and OH bands at 2.8 μ and 3.0 μ. The substance was water soluble and the solution showed an alkaline green coloration on pH paper.

Anal. Calcd. for $C_{11}H_{19}O_2N$: C, 67.0; H, 9.73. Found: C, 67.1; H, 9.80.

2-Acetyl-5-oxodecahydroisoquinoline (*18*) (**probably** *trans*).—To a solution of 22.9 g. (0.116 mole) of hydroxyamide *17* in 120 ml. of C.P. benzene cooled to 6° there was added with stirring a solution of 12.2 g. of sodium dichromate dihydrate in 9.4 ml. of glacial acetic acid, 17 ml. of concd. sulfuric acid, and 52 ml. of water during 1 hr.[34] Ice bath cooling and stirring were maintained an additional 1.25 hr. and then the reaction mixture was brought to room temperature with a water bath and 2 ml. of methanol was added to destroy excess chromate. After 15 min., 100 ml. of ether and solid potassium carbonate were added to the point where pH paper reacted neutral or slightly basic. The organic layer was separated and combined with three to four ether extractions of the aqueous layer. Organic solution was washed with aqueous carbonate and then with saturated sodium chloride, and was dried over sodium sulfate. The ketone *18* was obtained upon distillation, 16.7 g. (75%), b.p. 154–157° (0.7 mm.). Infrared: no OH band, ketone C=O at 5.83 μ, disubstituted amide C=O at 6.11 μ, C—H bands at 3.31, 3.39, 3.47 μ.

The ketone gave a yellow-orange dinitrophenylhydrazone from dilute ethanol, m.p. 218–219°. Only one derivative appeared to be formed as even the crude initially precipitated dinitrophenylhydrazone melted at 218–219°. The indication was that the ketone was present in substantially one stereoisomeric form, probably that of *trans* configuration.

Anal. Calcd. for $C_{17}H_{21}O_5N_5$: C, 54.5; H, 5.65. Found: C, 54.4; H, 5.77.

2-Acetyl-5-oxo-6-oxymethylenedecahydroisoquinolene.—Sodium methoxide was prepared from 2.5 g. (0.11 g.-atom) sodium and absolute methanol. Excess methanol was removed *in vacuo* and the solid was dried 2 hr. at 150° (1 mm.).

The sodium methoxide was covered with 100 ml. of cold dry benzene and 16 ml. (5 equiv.) of freshly distilled ethyl formate in 50 ml. of dry ether. The mixture was cooled in an ice bath and 7.2 g. (0.037 mole) of 2-acetyl-5-oxodecahydroisoquinoline (*18*) in 160 ml. dry ether was added under

(32) R. Weissgerber, *Ber.*, **47**, 3175 (1914).

(33) H. R. Billica and H. Adkins, *Org. Syn.*, **29**, 24 (1949), Note 1.

(34) W. S. Johnson, C. D. Gutsche, and D. K. Banerjee, *J. Am. Chem. Soc.*, **73**, 5464 (1951).

nitrogen. The suspension was stirred (N_2) at 0–5° for 2 hr. then at room temperature overnight (10–11 hr.). The reaction was worked up by adding cold water and stirring until all solids were dissolved. The aqueous layer was separated, saturated with ammonium chloride, neutralized with 1.1 equivalents of glacial acetic acid, and extracted exhaustively with chloroform.

The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under vacuum on the steam bath to a thick, gummy material 8.5 g. (100%), which gave a deep red-purple ferric chloride coloration. The formyl derivative was used directly in the preparation of the 6-ethylenedithioketal *24*, as in the following description.

2-Acetyl-5,6-dioxodecahydroisoquinoline 6-Ethylenedithioketal (*24*).—A mixture of the 8.5 g. of total crude formyl derivative of *18* prepared as immediately above, 14.5 g. of ethylene bis-*p*-toluenethiosulfonate, 20 g. of freshly fused potassium acetate, and 200 ml. of absolute ethanol was heated at reflux for 22 hr. under nitrogen. The alcohol was removed *in vacuo* and the residue was extracted into a mixture of water and benzene. The benzene layer was separated, then washed with water, and dried over magnesium sulfate. The benzene solution was passed through a silica gel chromatographic column and evaporated to 5.0 g. of viscous yellow oil which partially solidified on standing. Suction filtration gave 2.8 g. of a yellowish solid which was molecularly distilled at 0.5 mm. with an oil bath temperature of 225–235°. The distillate a viscous yellow oil, solidified on being triturated with ether. The solid was recrystallized from benzene–ligroin (b.p. 86–110°) to give 0.82 g. (8%) of a white solid, m.p. 135–136°, the dithioketal *24*. Infrared spectra (KBr disc) showed C=O bands at 5.89 μ and amide C=O at 6.14 μ.

Anal. Calcd. for $C_{13}H_{19}NO_3S_2$: C, 54.70; H, 6.71; N, 4.91. Found: C, 54.77; H, 6.86; N, 5.22.

5-Acetoxyisoquinoline.—5-Hydroxyisoquinoline (295 g.) was dissolved in acetic anhydride (400 ml.) and heated on the steam bath for 0.5 hr. The excess reagent was distilled at the water pump and the residue was taken up in chloroform and washed with sodium bicarbonate solution. Evaporation of the dried (Na_2SO_4) chloroform solution gave an oil which on being distilled afforded 320 g. (85%) pale yellow oil, b.p. 150–155° (0.3 mm.). On being triturated with ether it crystallized, m.p. 99–100°. This is undoubtedly an allotropic form of 5-acetoxyisoquinoline as previously it was reported[35] with m.p. 59–60°. The infrared showed no OH absorption and a strong C=O at 1775 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.57; H, 4.86; N, 7.48. Found: C, 70.2; H, 4.86; N, 7.54.

5-Hydroxyisoquinoline N-Oxide (*19*).—5-Acetoxyisoquinoline (270 g.) in 1 l. of glacial acetic acid was treated with 30% hydrogen peroxide (180 g.) and the solution was heated at 70–80° (care was necessary to prevent temperature rise above this range) until it gave a negative starch/potassium iodide (5–5.5 hr.). The acetic acid was distilled at the water pump, and the solid residue was treated with water and with sodium hydroxide until slightly basic (pH ~8). Ten grams of recovered 5-hydroxyisoquinoline was filtered off. On acidification to pH ~6.5, the product, 258 g. (m.p. 240–245°) was filtered off. Recrystallization from aqueous alcohol afforded creamy colored needles, m.p. 275.5°. Infrared spectra indicated strongly hydrogen bonded OH (3400 cm.$^{-1}$) and no C=O absorption. The oxide was readily soluble in dilute sodium bicarbonate solution and in dilute hydrochloric acid.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.85; H, 4.31; N, 8.66.

Treatment with alcoholic hydrogen chloride gave pale yellow crystals, which on recrystallization from alcoholic hydrogen chloride–ether afforded the **hydrochloride** of *19*, m.p. 208–210° (dec.)

(35) R. B. Woodward and W. v. E. Doering, *J. Am. Chem. Soc.*, **67**, 1860 (1945).

Anal. Calcd. for $C_9H_8O_2NCl$: C, 54.69; H, 4.09; N, 7.09. Found: C, 54.60; H, 4.05; N, 6.66.

5-Benzoxyisoquinaldo-1-nitrile (*20b*).—To a suspension of 10 g. of 5-hydroxyisoquinoline N-oxide in 200 ml. of water was added 10 g. of potassium cyanide. The oxide immediately dissolved and 30 ml. of benzoyl chloride was added slowly during 15 min. The solution became warm (in larger runs it was necessary to apply some external cooling) and a solid gradually separated. It was taken up in chloroform, and the chloroform extract was shaken several times with cold dilute sodium hydroxide, water, and dried (Na_2SO_4), Norite. Evaporation of solvent afforded an oil, which solidified on being triturated with alcohol. Filtration yielded the product *20b* as a white crystalline solid, 9.0 g. (53%) m.p. 148–149°. Recrystallization from alcohol raised the m.p. to 152–153°. Infrared absorption indicated C≡N 2250 cm.$^{-1}$, C=O at 1740 cm.$^{-1}$, and ester C—O—C at 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{10}O_2N$: C, 74.44; H, 3.68; N, 10.22. Found: C, 74.20; H, 3.29; N, 10.33.

5-Hydroxyisoquinaldo-1-nitrile. (*20a*).—The above benzoxynitrile *20b* (9.0 g.) was suspended in absolute ethanol (150 ml.) and saturated with dry hydrogen-chloride. After being refluxed for 6 hr., the ethanol was taken off *in vacuo*, the excess hydrogen chloride was neutralized with sodium bicarbonate solution, and the product was filtered off as a creamy solid, 5.5 g. (100%) m.p. 235–245°. Several recrystallizations from alcohol gave m.p. 269–270° (dec.). Infrared showed C≡N at 2250 cm.$^{-1}$ and no C=O absorption.

Anal. Calcd. for $C_{10}H_6O_2N$: C, 70.51; H, 3.56; N, 16.41. Found: C, 70.11; H, 3.70; N, 16.11.

5-Hydroxyisoquinaldic Acid (*21a*).—The benzoxynitrile *20b* (18 g.) was heated on a steam bath with 100 ml. of 3 *N* sodium hydroxide until dissolution was complete (2 hr.). Ammonia was given off. Acidification of the cooled solution until weakly acidic gave a solid which was washed several times with ether to remove benzoic acid. The product, 5-hydroxyisoquinaldic acid (*21a*), 11 g. (89%) m.p. 218°, could be recrystallized from water–Cellosolve as pale yellow needles, m.p. 219–220° (dec.). Infrared (KBr disc) indicated the zwitterionic form of *21a* with bands: OH and $-\overset{\oplus}{N}-H$ at 3300 cm.$^{-1}$ and 2600 cm.$^{-1}$ and $-COO^-$ at 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.48; H, 3.74; N, 7.41. Found: C, 63.16; H, 3.51; N, 7.70.

Treatment of the zwitterionic salt with alcoholic hydrogen chloride and evaporation of the solvent produced the **hydrochloride** of *21a* as orange needles, m.p. 192° (dec.), which was analyzed as a half-alcoholate. The infrared spectrum of the hydrochloride (KBr disc) showed a strong hydroxyl absorption at 3200 cm.$^{-1}$, a band at 1925 cm.$^{-1}$ (5.15 μ), and C=O at 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_8O_3NCl \cdot {}^1/_2\, C_2H_5OH$: C, 53.1; H, 4.40; N, 5.61. Found: C, 52.6; H, 4.29; N, 5.62.

Recrystallization of the hydrochloride from alcohol regenerated the free base *21a*.

5-Hydroxyisoquinaldic acid may also be prepared by aqueous alkaline hydrolysis of the nitrile *20a* and of the benzoxynitrile *20b:* 1.5 hr. heating on the steam bath with 10% sodium hydroxide followed by acidification to litmus. In the case of the benzoxynitrile hydrolysis, the product must be washed with ether to remove the concomitant benzoic acid.

Ethyl 5-Hydroxyisoquinaldate (*21b*).—The hydroxy acid *21a* (12 g.) in 200 ml. of absolute alcohol was saturated with dry hydrogen chloride and refluxed 12 hr. The alcohol was taken off *in vacuo* and the cooled residue was taken up in ethyl acetate and washed with 50 ml. of 5% sodium bicarbonate. Acidification of the bicarbonate solution gave 0.8 g. of recovered acid, while evaporation of the organic phase produced a solid, which was recrystallized from dilute alcohol

to give ethyl 5-hydroxyisoquinaldate (*21b*), 10.7 g. (75%),[36] m.p. 148–151°; vacuum sublimation gave a m.p. 153–154°. Infrared showed C=O at 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.34; H, 5.11; N, 6.45. Found: C, 66.25; H, 5.19; N, 6.60.

Ethyl 1,2,3,4-Tetrahydro-5-hydroxyisoquinaldate (*22a*).—The above ester *21b* (1.1 g.) was added to prereduced platinum oxide (0.3 g.) in 50 ml. of glacial acetic acid. Hydrogenation proceeded rapidly at room temperature and atmospheric pressure, and after 1 hr. 2 molecular equivalents of hydrogen had been absorbed, whereupon the hydrogenation stopped abruptly. The filtered water clear solution was evaporated *in vacuo*. Addition of a little water yielded the product as fine white needles, 1.1 g., m.p. to 202–203°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.13; H, 6.85; N, 6.33. Found: C, 65.06; H, 7.01; N, 6.50.

Ethyl 2-Acetyl-5-hydroxy-1,2,3,4-tetrahydroisoquinaldate. (*22b*).—The tetrahydrohydroxy ester *22a* (0.90 g.) in warm absolute methanol (50 ml.) was treated with 2 ml. of acetic anhydride in small portions over 10 min. Methanol and methyl acetate were removed *in vacuo* and the product was taken up in ether and washed with a little dilute sodium bicarbonate solution. Several extractions with ice cold 2 *N* sodium hydroxide solution extracted the phenolic material. Acidification of the alkaline aqueous solution afforded an oil which solidified forthwith, m.p. 143–145°, 0.85 g. (85%). Recrystallization from aqueous alcohol gave m.p. 148–149.0°. Infrared spectra showed two carbonyl bands at 1730 cm.$^{-1}$ and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.85; H, 6.52; N, 5.32. Found: C, 63.83; H, 6.47; N, 5.48.

In subsequent hydrogenations of ethyl 1,2,3,4-tetrahydro-5-hydroxyisoquinaldate it was found expedient to acetylate the hydrogenation product directly to *22b* without intermediate isolation of *22a*.

Ethyl 2-Acetyl-5-hydroxydecahydroisoquinaldate (*23*).—The tetrahydro ester-amide *22b*. (7.0 g.) in 50 ml. of absolute alcohol containing one teaspoonful W-7 Raney nickel[33] and one sodium hydroxide pellet was hydrogenated at 180° and 2000 p.s.i. After 12 hr. the hydrogenation was virtually complete, the catalyst was filtered off, the alcohol removed *in vacuo*, and the resulting oil was distilled: 6.0 g. (85%), b.p. 200° (0.4 mm). The product *23* was a pale yellow glass which failed to crystallize and was readily soluble in water and somewhat hygroscopic. Infrared spectra showed no aromatic bands, OH at 3450 cm.$^{-1}$, and two C=O bands at 1740 cm.$^{-1}$ and 1650 cm.$^{-1}$. This alcohol was characterized as the ketone, into which it was converted as in the immediately following description.

1-Carbethoxy-2 Acetyl-5-oxodecahydroisoquinoline (*2b*). (a) **Chromic Acid in Pyridine Method.**[37] A solution of 10 g. of ethyl hydroxydecahydroisoquinaldate *23* in 70 ml. of pyridine was added to a cold (5%) suspension of chromic acid dipyridine complex in pyridine, prepared from the slow and cautious addition of 15 g. of chromic acid to 150 ml. of pyridine at 15–25°. The reaction mixture was stirred for 3 hr. at ice bath temperature and then at room temperature overnight. Ether (1 l.) was added and the chromia was filtered off and washed several times with ether. The combined ethers were evaporated to dryness *in vacuo*. The residual oil was taken up in ether and washed with a little 3 *N* hydrochloric acid saturated with sodium chloride and then with saturated sodium chloride and dried (Na_2SO_4). Evaporation of this solution afforded the product *2b*, 7.6 g. (77%), b.p. 175° (0.1 mm). The ketone *2b* was a glass and was inclined to be somewhat hygroscopic. Infrared spectra showed three C=O bands at 1742 cm.$^{-1}$ (ester), 1721 cm.$^{-1}$ (ketone), and 1650 cm.$^{-1}$ (amide).

The **dinitrophenylhydrazone** was prepared from an aqueous solution of dinitrophenylhydrazine hydrochloride, m.p. 90–92°. It decomposed on attempts at recrystallization.

Anal. Calcd. for $C_{20}H_{25}O_7N_5$: C, 53.68; H, 5.64; N, 15.65. Found: C, 53.83; H, 5.68; N, 15.59.

(b) **Chromic Acid in Acetone Method.**[21b]—The alcohol *23* (2.3 g.) was dissolved in 100 ml. of acetone (distilled from potassium permanganate) and 1.5 ml. of an 8 *N* chromic anhydride solution prepared according to ref. *21b* was added to the solution, which was then allowed to stand at room temperature for 20 min. The excess oxidizing power was reduced with a few drops of an aqueous bisulfite solution and the acetone solution was filtered from inorganic salts after the addition of one gram solid sodium bicarbonate and a little anhydrous sodium sulfate. Evaporation of the acetone and distillation produced the ketone *2b*, 1.6 g. (70%), b.p. 174–175° (0.1 mm.).

1-Carboxy-2-acetyl-5-oxodecahydroisoquinoline (*2a*).—The above ester *2b* (4.5 g.) was dissolved in 30 ml. of water and 3 g. of sodium hydroxide was added. The solution was heated on the steam bath for 20 min. The cooled solution was heated on the steam bath for 20 min. The cooled solution was acidified with concentrated hydrochloric acid, saturated with ammonium chloride, and extracted with five 25-ml. portions of chloroform. The combined extract was dried (Na_2SO_4) and evaporated to produce the keto acid amide *2a*, which was crystallized from benzene, 3.6 g. (90%), m.p. 170–173°. Slow recrystallization from benzene containing a few drops of ethanol raised the m.p. to 172–173°. Infrared absorption (KBr disc) showed two C=O bands at 1725 cm.$^{-1}$ (5.80 μ) and 1590 cm.$^{-1}$ (6.29 μ).[38]

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.23; H, 7.18; N, 5.85. Found: C, 60.61; H, 7.15; N, 5.91.

5-Nitroisoquinaldic Acid.—A solution of 5 g. of isoquinaldic[12] acid in 20 ml. of conc. sulfuric acid was cooled to 0° and to this was added conc. sulfuric acid (20 ml.) containing 3.0 g. of potassium nitrate dropwise over 1 hr. The reaction was kept at 30–40° for 5 hr., poured over ice, and neutralized with sodium hydroxide to pH ~ 4. The product precipitated and was filtered from the cold solution. Recrystallization from 1:1 isopropyl alcohol–water gave 5-nitroisoquinaldic acid, 6.0 g., (95%), m.p. 166°(dec.). Infrared spectra showed bands: $-\overset{+}{\underset{\diagdown}{\underset{/}{N}}}H$ (3.20 μ), C=O (5.88 μ), $COO^{\ominus}$ (6.10 μ) and NO_2 (6.55 μ).

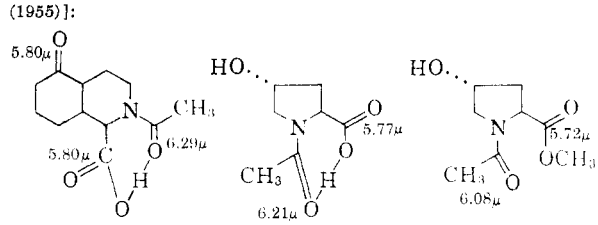
Anal. Calcd. for $C_{10}H_6O_4N_2$: C, 55.06; H, 2.77; N, 12.84. Found: C, 55.19; H, 2.99; N, 12.90.

Decarboxylation of 5-Nitroisoquinaldic Acid.—As proof of structure, the above nitroisoquinaldic acid (0.30 g.) was heated with 0.1 g. copper chromite at 250° for 15 min. The product was leached with 5 *N* hydrochloric acid. The acid extract was treated with Norite, filtered, and made basic with concentrated ammonia. Precipitated nitroisoquinoline, 0.25 g., had m.p. 106–107°, after recrystallization from aqueous alcohol, and undepressed on mixed melting with authentic 5-nitroisoquinoline. The picrates of both samples melted identically [216–217° (dec.)] and did not depress each other. Infrared spectra were also identical.

(36) A higher yield is obtained on 20 hr. reflux: private communication, Dr. Burris Tiffany, the Upjohn Company, Kalamazoo, Mich.

(37) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(38) This value for amide carbonyl absorption is strongly suggestive of intramolecular hydrogen bonding, *viz:* as in the ester *2b* amide absorption was normal at (1650 cm.$^{-1}$) 6.06 μ (*vide supra*). This situation finds analogy with that in the case N-acetylhydroxyproline and ester thereof [B. Witkop and R. K. Hill, *ibid.*, **77**, 6592 (1955)]:



5-Aminoisoquinaldic Acid and Ethyl 5-Aminoisoquinaldate.—A solution of 9.0 g. of 5-nitroisoquinaldic acid in 250 ml. of acetic acid was hydrogenated over 1.0 g. of 10% palladium–charcoal at 3 atm. and 50°. After the theoretical quantity of hydrogen had been absorbed, the filtered solution was evaporated *in vacuo*. The amino acid gave a *picrate* from aqueous picric acid which could be recrystallized from water, m.p. 260° (dec.)

Anal. Calcd. for $C_{16}H_{11}O_9N_5$: C, 46.05; H, 2.66; N, 16.79. Found: C, 45.93; H, 2.45; N, 16.81.

The hydrogenation residue above was taken up in 300 ml. of absolute ethanol, saturated with dry hydrogen chloride, and refluxed for 2 hr. The alcohol was evaporated and the residue was made weakly alkaline with aqueous ammonia. Ether extraction and distillation afforded ethyl 5-aminoisoquinaldate, 7.0 g., b.p. 190° (0.5 mm.). Infrared spectra showed C=O at 5.78 μ (1730 cm.$^{-1}$).

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.46; H, 5.65; N, 12.88.

***o*-Vanillin Benzyl Ether** (*26*).—A mixture of 262 g. of *o*-vanillin,[24] 240 g. of benzyl chloride, 150 g. of anhydrous potassium carbonate, and 650 ml. of methanol was refluxed with mechanical stirring for 11 hr. Most of the methanol was taken off *in vacuo* with stirring and the residue was taken into water and ether. The ether solution, combined with additional ether extraction of the aqueous layer, was washed with 2 *N* sodium hydroxide solution till no further phenolic material remained, with water, and finally with saturated sodium chloride solution. It was treated with Norite, dried over magnesium sulfate, and distilled to yield *o*-vanillin benzyl ether, 394 g. (95%), b.p. 166–168° (1.00 mm.).

2-Benzyloxy-3-methoxy-β-nitrostyrene (*27*).—A mixture of 24.2 g. (0.10 mole) of *o*-vanillin benzyl ether, 6.5 g. of nitromethane, 0.5 g. of methylamine hydrochloride,[39] 0.25 g. of anhydrous sodium carbonate and 10 ml. of absolute ethanol was allowed to stand 3 days, whereupon it was scratched and seeded. Yellow crystals developed and, after 2 more days, the well cooled mass was filtered and washed with cold dilute ethanol; 19 g. of air dried material was obtained. It could be crystallized from methanol, m.p. 72–73°.

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.40; H, 5.29; N, 4.92. Found: C, 66.98; H, 5.18; N, 5.19.

β-(2-Benzyloxy-3-methoxyphenyl)ethylamine (*28*).—The one step reduction of the β-nitrostyrene *27* to the β-phenylethylamine *28* was effected by means of lithium aluminum hydride.[40] Thirty grams of the nitrostyrene *27* was reduced with a solution of 20 g. of lithium aluminum hydride in 1200 ml. of dry ether, using the Soxhlet extraction technique for adding the compound to be reduced. Total reflux time of 36 hr. was required. The excess hydride was decomposed by the cautious dropwise addition of water to the cooled reaction mixture followed by addition of *ca.* 50 ml. of 40% potassium hydroxide solution. The ether solution was decanted from the inorganic matter and was exhaustively extracted with 2.5 *N* hydrochloric acid until no more amine was indicated in the extracts. The aqueous acidic solution was extracted once with ether and was than made alkaline to regenerate the amine, which was extracted with ether, dried (Na_2SO_4) and distilled to yield the amine *28*, 19.0 g. (70%), b.p. 154–159° (0.5–0.7 mm.). It was treated directly with formaldehyde as in the following description.

5-Benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (*29*).—A mixture of 2.5 g. of the amine *28* above and 0.9 g. 37% formalin (1.1 equivs. of formaldehyde was heated on the steam bath for 1 hr. It was then allowed to cool, and 3 ml. of water and 1 ml. of conc. hydrochloric acid were added and the reaction was allowed to stand overnight at ordinary temperatures. The water was taken off *in vacuo* without application of heat and a crystalline residue remained, to which when concd. hydrochloric acid was added the **hydrochloride** of *29* crystallized. It was filtered and washed with conc. hydrochloric acid. It was recrystallized from ethanol–acetone, m.p. 217–218°.

Anal. Calcd. for $C_{17}H_{20}O_2NCl$: C, 66.80; H, 6.61. Found: C, 66.48; H, 6.44.

The free base, the tetrahydrobenzyloxymethoxyisoquinoline, *29*, was regenerated from the hydrochloride above by the addition of alkali and was recrystallized from dilute methanol, m.p. 106.5–107.5°.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.80; H, 7.08. Found: C, 75.49; H, 6.74.

The base *29* could be acetylated to an N-acetyl derivative (m.p. 81–83°) which in turn could be debenzylated over palladium–charcoal to the corresponding phenolic substance but these derivatives were not investigated further as the need for them had passed.

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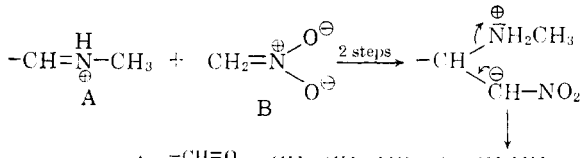
(39) The claim had been made by Knoevenagel [Knoevenagel and Walter, *Ber.*, **37**, 4502 (1904); see also Gulland and Virden, *J. Chem. Soc.*, 1791 (1929)] that only primary amines and not secondary or tertiary ones were effective in promoting condensation of an aromatic aldehyde and nitromethane. This has been borne out in a former investigation (V. Georgian, Ph.D. dissertation, Harvard University, 1950) in which it was found that N-ethylethanolamine, a moderately strong base, was ineffective in promoting condensation between *m*-methoxybenzaldehyde and nitromethane, which could be accomplished quantitatively, albeit slowly, with a trace of methylamine. It appears that a Schiff salt (*A*) is the necessary intermediate and not merely the ionization of the nitromethane (*B*), *viz:*



(40) F. Ramirez, *J. Am. Chem. Soc.*, **72**, 2781 (1950).