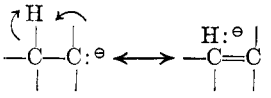
of the reactive species in both reactions, regardless of its form.

The resonance stabilization of carbanions (free or incipient) that has been proposed by Polanyi[21] could explain the order of the reaction rates and decomposition voltages if the results obtained by assuming E° a constant are used.



It thus appears that all four sets of data can be tied together in a common ground—the concentration, or availability of, a common ion.

Work is presently being carried out using both conductivity measurements and dielectric constant measurements as a method of following the rates of reaction of Grignard reagents with various substrates.

TABLE IV

RELATIVE POTENTIALS[a] OF ALKYLMAGNESIUM BROMIDES AT 1*M* CONCENTRATIONS

R	E.m.f.[16]	E_D^{19}
Et	1.24[b]	1.28[b]
i-Pr	1.27[b]	1.07[b]
t-Bu	1.41[c]	0.87[b]
n-Pr	1.23[c]	1.42[b]
i-Bu	1.21[c]	1.29[b]

[a] Uncorrected for Pt-saturated calomel electrode potentials. [b] Values for 1 molar solution. [c] Extrapolated from range 0.05–0.2*M* solutions.

Acknowledgment. The authors would like to thank E. H. Sargent and Company for the loan of a Sargent Model V Chemical Oscillometer.

CINCINNATI 21, OHIO

(21) E. C. Bangham, M. G. Evans, and M. Polanyi, *Trans. Faraday Society*, **37**, 377 (1947).

[CONTRIBUTION NO. 1486 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Synthesis of (−)-6-*exo*,7-*endo*-Dihydroxy-3-tropanone; An Optically Active Product from a Robinson-Mannich Condensation[1]

ROBERT STERN[2] AND HARRY H. WASSERMAN

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Oxidation of 3,4-monoacetone-D-mannitol (I) by means of lead tetraacetate, followed by acid hydrolysis and treatment of the resulting L-tartardialdehyde solution with acetone dicarboxylic acid and methylamine hydrochloride, resulted in the formation of (−)-6-*exo*, 7-*endo*-dihydroxy-3-tropanone (IVa).

We wish to report the synthesis of (−)-6-*exo*, 7-*endo*-dihydroxy-3-tropanone[3,4] ("levorotatory teloidinone"), using D-mannitol as starting material, and involving L-tartardialdehyde[6] as an intermediary product. Our results, along with other recent work in this field,[7] show that a Mannich-type reaction involving an enolizable optically active aldehyde, R′—CH(R)—CHO, can lead to an optically active condensation product.

Partial hydrolysis of triacetone-D-mannitol,[8] obtained from D-mannitol and acetone, yielded 3,4-monoacetone-D-mannitol,[9] I, m.p. 86–88°, $[\alpha]_D^{20.0}$ +23.0. The oxidation of I with pure lead tetraacetate according to the procedure of Fischer and Appel afforded acetone-L-tartardialdehyde[10] (acetone-D-α,α'-dihydroxysuccindialdehyde), II, an intermediate which was not isolated. Hydrolysis of the crude reaction product with 0.1*N* sulfuric acid, to

(1) Presented at the 131st Meeting of the American Chemical Society in Miami, Fla., April 8, 1957.

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(3) We are using the *exo-endo* designations in describing derivatives of tropane (*N*-methyl-8-aza-[1, 2, 3]-bicyclooctane) in accordance with the usage of K. Alder and H. A. Dortmann, *Ber.* **86**, 1545 (1953). An alternate nomenclature used for tropane derivatives has been adapted from steroids by G. Fodor and K. Nador, *J. Chem. Soc.*, 722 (1953).

(4) The absolute configuration of this optically active compound is identical to that of L(−)-tartaric acid.[5] It can be called R(−)-6,7-dihydroxy-3-tropanone, according to a general stereochemical nomenclature recently proposed by R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(5) (a) K. Freudenberg, "Stereochemie", Franz Deuticke, Leipzig and Wien, 1933, p. 668; (b) C. D. Nenitzescu, *J. Chem. Educ.*, **34**, 147 (1957).

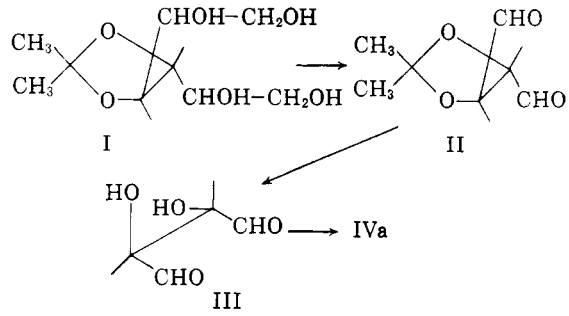
(6) An alternative designation of this compound is D-α,α'-dihydroxysuccindialdehyde.

(7) Since we first reported our results [see footnote (1)] E. Hardegger and H. Furter, *Helv. Chim. Acta*, **40**, 872 (1957), have published the account of an independent synthesis of S(+)-6,7-dihydroxy-3-tropanone from D(+)-tartaric dialdehyde. Their condensation product is the dextrorotatory enantiomer of the one we have prepared. Furthermore, K. Zeile and A. Heusner, *Ber.*, **90**, 1869 (1957), have recently published an independent synthesis of (−)-alloteloidinone, a product which appears to be identical with our material.

(8) E. Fischer, *Ber.*, **28**, 1167 (1895).

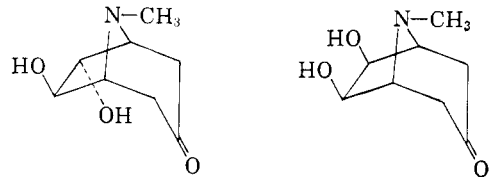
(9) L. F. Wiggins, *J. Chem. Soc.*, 13 (1946).

(10) H. O. L. Fischer and H. Appel, *Helv. Chim. Acta*, **17**, 1574 (1934).



remove the isopropylidene protecting group (*cf.* III), was followed by treatment with excess methylamine hydrochloride and excess acetonedicarboxylic acid, under slightly modified conditions of the usual Robinson synthesis.[11] Extraction with ether and crystallization from isopropanol afforded the condensation product IVa in the form of large white prisms, m.p. 183.5–185.0°, $[\alpha]_D^{25.0}$ −37.64 ± 0.90 (in water).

The melting point and the optical activity of this material show clearly that it does not possess the stereochemical structure of the known teloidinone,[11] V, a *meso* compound. The infrared absorption spectrum of the levorotatory adduct in the solid state (potassium bromide) is very similar to that of an authentic sample of (±)-6,7-dihydroxy-3-tropanone, IVb, recently prepared by Sheehan.[12] In pyridine solution, on the other hand, our optically active material and Sheehan's compound[12] exhibit completely superimposable infrared absorption spectra. The structure of adduct IVa is thus (−)-6-*exo*,7-*endo*-dihydroxy-3-tropanone.



The following observations are significant in connection with these experiments:

(a) No optically inactive tropane derivative, whether it be *racemic* or *meso* could be isolated from the reaction mixture in repeated condensations utilizing the above components. The fact that optical integrity was thus preserved shows that the Robinson synthesis and related Mannich-type condensations can take place without racemization of an optically active center adjacent to the aldehyde function.

(b) The successful synthesis of adduct IVa shows clearly that tropanone derivatives with substituents in the *endo*-configuration at C-6 or C-7 (both of which have their origin in the aldehyde component of the condensation, *cf.* IVa) can be formed[13] in the Robinson synthesis.[14]

EXPERIMENTAL[17]

*1,2,3,4,5,6-Triacetone-*D*-mannitol.* This compound, m.p. 67–68°, was prepared from commercial D-mannitol and acetone in the presence of sulfuric acid according to the procedure of Wiggins[9] and that of Fischer.[8] Our yield was 53% as compared to 75% reported by Wiggins.

*3,4-Monoacetone-*D*-mannitol* (I). The following modification of Wiggins' procedure[9] gave best results when adapted to a larger scale: 1,2,3,4,5,6-Triacetone-D-mannitol (60.4 g.; 0.2 mole) was dissolved in 1200 ml. of 70% acetic acid and the solution heated to 40° for 30 min. The solvent was then removed *in vacuo* at 40–50°, an operation that took 2 hr. The residue was taken up in 750 ml. of boiling acetone, the solution filtered from insoluble mannitol, concentrated to 250 ml. and poured into 1300 ml. of boiling benzene. Concentrating the solution to 700 ml. and cooling yielded 33.5 g. (75.4% yield) of white crystals, m.p. 75–84°. Three consecutive crystallizations from ethyl acetate and benzene raised the melting point to 86–88°. Wiggins[9] reported a melting point of 86–87° for this compound; Fischer and Appel,[10] and Irvine and Patterson[18] recorded 85° as the m.p.

*Oxidation of 3,4-monoacetone-*D*-mannitol* (I) *to* L*-tartardialdehyde*[6] (III). 3,4-Monoacetone-D-mannitol (22.22 g., 0.1 mole) was added to a solution of 88.6 g. (0.2 mole) of lead tetraacetate in 400 ml. of hot benzene, and the mixture was heated on the steam bath for about 5 min. with constant agitation. After a positive starch–iodide reaction was obtained, the benzene solution was cooled to 5°, filtered, and the precipitate washed with benzene. The solvent was removed from the combined benzene phase *as fast as possible* by distillation under reduced pressure (oil-pump vacuum) at a temperature (5°) just above the melting point of the mixture.

The dialdehyde residue, a viscous oil, was taken up in 150 ml. of 0.18*N* sulfuric acid, and the solution heated on the steam bath for a few minutes until all of the oil had dissolved. The solution was allowed to stand for about 3 hr. and was then filtered from the precipitated lead salts. Finally, the dialdehyde solution was concentrated to about 65 ml. under reduced pressure (oil-pump) and *without heating*, in order to remove the acetone formed during hydrolysis, and was brought to a *p*H of 5 by careful addition of solid sodium bicarbonate. The dialdehyde III was not isolated; it was used in the form of its aqueous solution for the subsequent Robinson condensation.

(11) (a) C. Schöpf and W. Arnold, *Ann.*, **558**, 109 (1947); (b) J. C. Sheehan and B. M. Bloom, *J. Am. Chem. Soc.*, **74**, 3825 (1952).

(12) An authentic sample of this compound was kindly made available to us by Professor J. C. Sheehan of the Massachusetts Institute of Technology. *Cf.* G. Fodor, *Tetrahedron*, **1**, 95 (1957).

(13) See in this connection: (a) K. Alder and H. A. Dortmann, *Ber.*, **86**, 1545 (1953); (b) J. Keberle and P. Karrer, *Helv. Chim. Acta*, **37**, 484 (1954).

(14) The possibility [G. Fodor, *Experientia*, **11**, 138 (1955)] that a 6-*endo*-substituted product may have been obtained previously, as a component of Stoll's synthetic valerinone,[15] is excluded, since on reduction, the latter affords an optically inactive material identical with the 3,6-dihydroxytropane, independently obtained by hydrogenolysis of scopolamine,[16] in which the exclusive *exo*-orientation of the 6-hydroxyl group has been firmly established.[16]

(15) (a) A. Stoll, B. Becker and E. Jucker, *Helv. Chim. Acta*, **35**, 1263 (1952); (b) A. Stoll, A. Lindenmann, and E. Jucker, *Helv. Chim. Acta*, **36**, 1506 (1953).

(16) G. Fodor and O. Kovacs, *J. Chem. Soc.*, 2341 (1953).

(17) All melting points are uncorrected and were taken on a Koffler block.

(18) J. C. Irvine and B. M. Patterson, *J. Chem. Soc.*, 898 (1914).

(−)-*6-exo,7-endo-Dihydroxy-3-tropanone*[3] (IVa). To an aqueous L-tartardialdehyde solution prepared, as described above, from 22.22 g. (0.1 mole) of 3,4-monoacetone-D-mannitol, there was added 29.2 g. (0.2 mole) of pure acetonedicarboxylic acid dissolved in a buffer prepared from 150 g. of sodium acetate and 425 ml. of distilled water. This was followed by the addition of 13.5 g. (0.2 mole) of pure methylamine hydrochloride dissolved in 30 ml. of distilled water. The very slightly yellow solution had a total volume of about 550–600 ml. and a *p*H of 5.2. It was allowed to stand for 7 days in a thermostat at 25.0°. A very slow evolution of carbon dioxide started after about 15 min. and the color of the solution darkened gradually.

After 7 days the *cooled* reaction mixture was saturated with solid potassium carbonate. The resulting deep-brown solution was extracted continuously with ether for 7 days. Large crystals separated from the ether extract, and a further small crop of crystals could be isolated by evaporating the solvent. The total weight of the crystalline residue was 3.2 g. (19% yield), m.p. 178–183.5°. Six consecutive crystallizations from isopropyl alcohol afforded pure IVa in the form of white prisms, constant melting point 183.5–185°, constant rotation (measured in a micropolarimeter) in water solution $[\alpha]_D^{25.0}$ −37.64 ± 0.90.

Anal. Calcd. for $C_8H_{13}O_3N$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.26; H, 7.39; N, 7.98.

The crystals were quite insoluble in ether, chloroform, carbon tetrachloride, carbon disulfide, acetonitrile, and in aliphatic and aromatic hydrocarbons. They were slightly soluble in, and could be recrystallized from, isopropyl alcohol, acetone, and dioxane (solubility approximately 30 g./l.), and dissolved readily in ethyl alcohol and pyridine. The compound was infinitely soluble in water.

The aqueous solution from which the major part of IVa had been removed by ether extraction was evaporated to dryness, and the carefully dried residue, largely inorganic in nature, repeatedly refluxed with several portions of absolute ethyl alcohol. Although both *racemic* IVa and *meso*-teloidinone are very soluble in hot ethyl alcohol, no appreciable quantities of any organic material could be isolated from the alcoholic extracts.

Acknowledgments. The authors wish to thank Professor James English, Jr., for helpful discussions. The financial assistance of the National Paraplegia Foundation in the form of a Postdoctoral Fellowship to one of us (R.S.) is most gratefully acknowledged.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE PASADENA FOUNDATION FOR MEDICAL RESEARCH]

Studies with Quinolines. I. Synthesis of Quinaldic Acid and Some of Its Amide Derivatives[1]

JEFFERSON W. DAVIS, JR.

Received June 9, 1959

Quinaldic acid has been prepared and isolated in quantitative yield by the acid catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile, using hydrobromic acid in acetic acid as the reaction medium. The use of the quinaldyl radical as a means of identification of primary and secondary amino groups has been demonstrated, and a number of quinaldoamides have been prepared and characterized.

Recent developments in the fields of nutrition and chemotherapy have resulted in a resurgence of interest in amino acids, peptides and proteins, and the need for more reagents for identification and isolation of these important substances has become of prime importance. 1-Fluoro-2,4-dinitrobenzene (FDNB), studied by Sanger[2–4] in his work on insulin, has been used extensively for the identification of amino acids, and particularly for the determination of the *N*-terminal residues of proteins and peptides. Subsequent workers[5] have prepared DNP-amino acids and studied some of their properties. Yields in many instances were low, and often no crystalline derivatives were obtained. The phthaloyl group[6] has also been used for the identification of amino compounds, but this reagent is limited and its use has not been extended to peptides.

The quinaldyl radical may be used effectively for the identification of primary and secondary amino groups. Amide derivatives are prepared very easily in semiquantitative yields, and have sharp characteristic melting points. These melting points are generally high—a fact which probably accounts for the highly crystalline form of these compounds.

Because of the difficulties involved in the preparation, isolation and purification of the quinaldic acids by existing methods, a thorough investigation of the synthesis of this important class of compounds was undertaken. The original synthesis of the quinaldic acids goes back to the year 1905 when Arnold Reissert[7] found that quinoline, in the presence of alkali cyanide and benzoyl chloride,

(1) The work in this paper was initiated in the Laboratories of Pharmacology of the Pasteur Institute, under the direction of Prof. J. Trefouel, and was supported in part by a grant from the Centre National de la Recherche Scientifique, Paris, France.

(2) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(3) F. Sanger, *Biochem. J.*, **40**, 261 (1946).

(4) R. R. Porter and F. Sanger, *Biochem. J.*, **42**, 287 (1948).

(5) K. R. Rao and Herbert A. Sober, *J. Am. Chem. Soc.*, **76**, 1328–31 (1954).

(6) John H. Bellman and William F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).

(7) A. Reissert, *Ber.*, **38**, 1610 (1905).