(−)-*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.

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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).

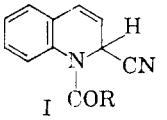
(4) R. R. Porter and F. Sanger, *Biochem. J.*, **42**, 287 (1948).

(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).

formed an addition compound which, on treatment with mineral acid, gave quinoline carboxylic acid and benzaldehyde. These addition compounds have subsequently been termed "Reissert compounds" and are generally formed by the addition of an acyl and cyano group to the azomethine linkage of certain *N*-heterocycles.



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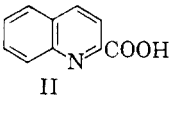

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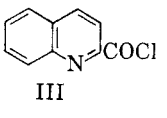
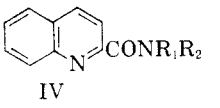


III

Compounds of the type (I) have been the subject of extensive investigations in recent years,[8] and particular attention has been centered about the formation of aldehydes from the acid catalyzed hydrolysis of these intermediates. In many instances the yields of aldehydes were greater than 90% of theory, but yields of acids were often low and not much superior to those obtained by Reissert. Other investigators[9-11] have prepared quinaldic acid by modifications of Reissert's method and other procedures.

We have found that compounds of the type (I) undergo complete hydrolysis with the evolution of heat in mixtures of aqueous hydrobromic acid and acetic acid. The formation of aldehydes and the corresponding acids is complete within 20 minutes and, with the exception of a trace of pigmented material, these are the only products detected. The acid hydrobromide formed is insoluble in the reaction medium, and is obtained in a very pure state by simple filtration. Yields of from 95 to 100% of pure acid based on (I) were obtained when the acid hydrobromide was treated with excess of ammonium hydroxide and then with excess of acetic acid. High yields of aldehydes were also obtained.

Although quinaldic acid (II) is an amino acid, it may be converted to the acid chloride (III) on treatment with thionyl chloride without formation of the hydrochloride. This acid chloride is stable under ordinary conditions and is only slightly soluble in water, which decomposes it on long standing. It reacts quantitatively with primary and secondary amino compounds, in aqueous or non-aqueous media, with evolution of heat and formation of amide adducts (IV).[12]



IV

EXPERIMENTAL

1-Benzoyl-1,2-dihydroquinaldonitrile(I)R=C_6H_5. This compound was prepared by the procedure of Reissert[7] in yields of from 90 to 95% of theory. It may be advantageously purified by recrystallization from 60% aqueous acetone. The colorless prismatic needles melted at 155°.

Quinaldic acid hydrobromide. Twenty-five grams of the above purified 1-benzoyl-1,2-dihydroquinaldonitrile was suspended in 25 ml. of glacial acetic acid. To this suspension was added 25 ml. of aqueous hydrobromic acid (d = 1.7). There was an immediate evolution of heat and after several minutes the red-brown reaction mixture was warmed under reflux for 15 minutes. On cooling, the monohydrate of quinaldic acid hydrobromide crystallized. The light brown crystals were collected by filtration with suction and were thoroughly washed with glacial acetic acid and then with ether. After drying under vacuum over sodium hydroxide, the product weighed 28.0 grams and melted with decomposition at 220–224°. When the residue obtained from evaporation of a decolorized aqueous solution of the hydrobromide was recrystallized from 90% acetic acid, the pale yellow crystals melted at 220–221° (dec.):

Analysis:	C%,	H%,	N%,	Br%,
Cal. for $C_{10}H_8O_2BrN$, H_2O	44.10	3.68	5.15	29.40
Found	44.22	3.78	5.22	29.16
After drying at 110° in vacuum over P_2O_5 for 24 hours:				
Found	46.76	3.17		31.42
Cal. for $C_{10}H_8O_2BrN$	47.10	3.14		31.40

Quinaldic acid (II). The quinaldic acid hydrobromide monohydrate obtained above was converted to the free acid as follows: 28 gm. of the crude material were dissolved in 50 ml. of hot water and treated with 0.5 gm. of norite. To the almost colorless solution obtained upon filtration was added 20 ml. of concentrated ammonium hydroxide. The ammonium salt, which is only sparingly soluble under these conditions and which may be isolated by filtration was made to dissolve by heating the mixture to boiling. The hot solution, which contained a small amount of insoluble pigmented material, was treated with a small quantity of norite. After filtration, 20 ml. of glacial acetic acid was added to the colorless solution, and on cooling the quinaldic acid dihydrate separated as long colorless needles. The acid was washed several times with ice water, and after drying at 60° for 24 hr. the product weighed 20.1 gm., 96% of theory, and melted at 155–156°. Other runs on a smaller scale gave almost quantitative yields of acid based on Reissert's compound. On recrystallization from 75% acetic acid, the melting point was raised to 156.5–157°. A sample for analysis was dried at 100° over P_2O_5 for 24 hr.

Analysis:	N%
Cal. for $C_{10}H_7O_2N$	8.00
Found	8.22

The melting point was not depressed when the above prepared acid was mixed with an authentic sample of quinaldic acid.

Benzaldehyde. In order to demonstrate that benzaldehyde, and not benzoic acid, was formed in the hydrolysis medium used for the conversion of Reissert's compound to the corresponding acid, the aldehyde was isolated and distilled. An excess of water was added to the mother liquors obtained after removal of the quinaldic acid hydrobromide from the

(8) W. E. McEwen and R. Lynn Cobb, *Chemical Reviews*, **55**, 511 (1955).

(9) Thomas W. J. Taylor, *J. Chem. Soc.*, 1110–11 (1929).

(10) Campbell et al., *J. Am. Chem. Soc.*, **68**, 1841 (1946).

(11) Hammick, *J. Chem. Soc.*, **123**, 2883 (1923).

(12) These amide derivatives of quinoline carboxylic acid are being studied to determine their action against certain types of tumors and bacteria. Since chelation is possible in many instances, it is felt that they may have some effect on the metabolism of inorganics in the cell. The results of this study will be reported elsewhere.

TABLE I

YIELDS, PHYSICAL PROPERTIES, AND ELEMENTAL ANALYSIS[a] OF SOME AMIDE DERIVATIVES OF QUINALDIC ACID

Amine[b]	M.P. °C.[c]	Crystallization solvent	Crystalline Form	Molecular Formula	% Carbon		% Hydrogen		% Nitrogen		Number[d]
					Cal.	Found	Cal.	Found	Cal.	Found	
2-Aminoethanol	107–108	Ether	Colorless elongated prisms	$C_{12}H_{12}O_2N_2$	66.67	66.98	5.54	5.46	12.93	12.60	3522
Alanine ethyl ester	80–81	Petroleum ether	Colorless prisms	$C_{15}H_{16}O_3N_2$	66.30	66.72	5.88	5.86	10.30	10.28	3521
Alanine	123.5–124	Chloroform petroleum ether	Colorless plates	$C_{13}H_{12}O_3N_2$	63.63	66.71	4.92	5.30	11.47	11.72	3520
Glycine ethyl ester	79.5–80	Ligroin	Colorless plates	$C_{14}H_{14}O_3N_2$	65.10	64.95	5.43	5.22	10.85	10.88	PF 200
Glycine	188–190	Methanol-water	Colorless plates	$C_{12}H_{10}O_3N_2$	62.60	62.53	4.35	4.38	12.20	12.49	3515
Aniline	139.5–140	Isopropyl-ether	Colorless needles	$C_{16}H_{12}ON_2$	77.50	77.87	4.83	4.88	11.30	11.24	3519
Phenylalanine ethyl ester	72–72.5	Ether-petroleum ether	Colorless needles	$C_{21}H_{20}O_3N_2$	72.41	72.76	5.74	4.67	8.04	7.80	PF 60
Phenylalanine	172.5–173	Methanol	Prismatic needles	$C_{19}H_{16}O_3N_2$	71.25	71.02	5.00	4.91	8.75	8.70	3514
N-Methylaniline	144–146	Ligroin	Prismatic needles	$C_{17}H_{14}ON_2$	77.90	78.23	5.35	5.54	10.70	10.65	3511
p-Tulidine	109.5–110	Ligroin	Long needles	$C_{17}H_{14}ON_2$	78.00	77.95	5.34	5.23	10.70	10.79	3510
p-Chloroaniline	135–135.5	Isopropyl–ether	Rectangular prisms	$C_{16}H_{11}ON_2Cl$	67.90	68.09	3.90	3.87	9.90	9.93	3509
o-Nitroaniline	179.5–180	Isopropyl ether	Yellow needles	$C_{16}H_{11}O_3N_3$	65.50	65.56	3.76	3.82	14.33	14.32	3512
Norleucine	143–144	Chloroform–petroleum ether	Small plates	$C_{16}H_{18}O_3N_2$	67.20	67.18	6.30	6.31	9.80	9.67	3513
Glycylglycine	229–230	Methanol	Short needles	$C_{14}H_{13}O_4N_3$	58.63	58.90	4.53	4.76	14.62	14.43	3516
Dicyclohexylamine	140–141	Isopropyl-ether	Colorless needles	$C_{22}H_{28}ON_2$	78.57	78.80	8.33	8.00	8.33	8.50	PF 110
Hydrazine	250–251	Chloroform-petroleum ether	Short needle clusters	$C_{16}H_9ON_3$	64.17	64.32	4.81	5.00	22.46	22.70	PF 113
Glycyl-L-valine	170–17015	Chloroform petroleum ether	Prismatic needles	$C_{17}H_{19}O_4N_3$	62.00	62.40	5.77	5.81	2.75	13.10	PF 114

[a] The microanalyses were carried out in the Laboratories of Pharmacology at the Pasteur Institute, Paris, France, under the direction of J. Trefouel. [b] Only racemic amino acids were used except in the case of #PF 114, glycyl-L-valine. [c] All melting points were taken by the capillary method and are uncorrected. [d] Compounds with numbers greater than three thousands are Pasteur Institute catalogue numbers; others are catalogue numbers of the Pasadena Foundation for Medical Research.

original reaction mixture, and the oil was taken into ether. The ethereal solution was washed with water until the washings were free of acid. On drying and removal of solvent, the dark red oil was distilled under reduced pressure. The fraction, distilling at 42–44° and 1 mm., was collected and weighed 9.5 gm. or 87% of theory. It was shown to be 98–100% pure benzaldehyde by its reaction with 2,4-dinitrophenylhydrazine. The hydrazone melted at 236–237°. The melting point did not change when the material was mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of benzaldehyde.

Quinaldyl chloride. Anhydrous quinaldic acid[13] was converted to the acid chloride by treatment with an excess of thionyl chloride (Eastman White Label) after the procedure of Besthorn and Ibele.[14] Seventeen and three-tenths grams of the anhydrous acid were suspended in 140 ml. of thionyl chloride and the mixture was heated on a water bath until evolution of HCl ceased. The excess thionyl chloride was removed under reduced pressure and the bright red crystalline mass of quinaldyl chloride recrystallized from ether. Eighteen grams of long yellow needles which melted at 96–97° were obtained.

The compounds listed in Table I which follows were prepared by two different procedures, depending upon the use of aqueous or non-aqueous reaction media. These are designated as *Procedure A* and *Procedure B*, and are described below.

Procedure A: Ten millimoles of the amino acid, peptide, etc., were dissolved in 20 ml. of normal sodium hydroxide and cooled to 0–10°. The solution was stirred, and 10 millimoles of quinaldic acid were added over a period of about 10 minutes. The cooling bath was removed and the mixture was allowed to come to room temperature. The clear orange solution was treated with a small amount of norite and filtered. On acidification with 10 ml. of normal hydrochloric acid an oil precipitated, which usually crystallized on standing. The crystals were collected by filtration and dried in air. When the oil formed on acidification did not crystallize, it was extracted with methylene chloride and dried. On removal of solvent and scratching with a glass rod, crystals were formed. Yields were from 95–100% of theory. The material was recrystallized from the appropriate solvent. In general, the quinaldyl amino acids will crystallize from chloroform–petroleum ether, but some of them may be crystallized from alcohol water.

Procedure B: Ten millimoles of amine, amino acid ester, etc., were dissolved in 10 ml. of methylene chloride to which had been added 10 millimoles of triethylamine or other tertiary base.[15] The solution was cooled to 0–10° and 10 millimoles of quinaldyl chloride was added over a period of 10 minutes. After the reaction mixture was allowed to come to room temperature it was washed well with water, dried, and treated with norite. The solvent was removed under reduced pressure, and the residual oil crystallized on being scratched with a glass rod. The yields were similar to those obtained in *Procedure A* above. The quinaldyl amides usually crystallize from petroleum ether (B.P. 60–100°) or isopropyl ether. Water sometimes interferes with the crystallization.

It is of interest to note that the presence of a hydroxyl group in the amino compound does not interfere with the reaction under the conditions described above. This is exemplified in the preparation of the ethanolamine adduct.

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(13) Obtained by heating several hundred grams of the hydrated material under high vacuum at 100° for 24 hr. This material, as well as quinaldyl chloride, is available commercially from Radio-Carbon Laboratories, Pasadena, California.

(14) E. Besthorn and J. Ibele, *Ber.*, **38**, 2127 (1905).

(15) When possible, it is preferable to use a 1 mole excess of the amine being acylated instead of the tertiary base.

[COMMUNICATION NO. 1999 FROM THE KODAK RESEARCH LABORATORIES]

The Preparation of Alicyclic Trioximes

DONALD C. BATESKY AND NEIL S. MOON

Received June 18, 1959

The reaction of cyclohexanone and its 4-methyl derivative with isoamyl nitrite results in the formation of the symmetrical dioximino ketones: 1,2,3-cyclohexanetrione-1,3-dioxime and 5-methyl-1,2,3-cyclohexanetrione-1,3-dioxime, instead of the expected keto monoximes. Oximation of the keto dioximes gives the corresponding trioximes. These trioximes give color reactions with various cations.

Alicyclic *vic*-dioximes, commonly prepared by the oxidation of alicyclic ketones with selenium dioxide to α-diketones followed by oximation,[1] and more recently by oximation of α-bromoalicyclic ketones,[2] have found widespread use as analytical reagents for nickel and palladium.[3] 1,2-Cyclohexanedione dioxime and its 4-methyl derivative, owing to their greater solubility than dimethylglyoxime in water, are excellent substitutes for this latter reagent in analysis.

To avoid the use of the toxic and expensive selenium dioxide, another route was taken to attempt the preparation of these reagents. Murakami and Yukawa[4] have reported the preparation of 1,2-cyclohexanedione dioxime by passing ethyl nitrite gas into a mixture of cyclohexanone and hydrochloric acid to obtain 1,2-cyclohexanedione monoxime, a solid decomposing at 227° which was then treated with hydroxylamine to yield the *vic*-dioxime melting at 186–187°. This method, because of the availability and low cost of starting materials, was selected in these Laboratories to pre-

(1) D. T. Hooker and C. V. Banks, *U. S. Atomic Energy Comm., ISC-597*, 113 pp. (1955).

(2) R. Belcher, W. Hoyle, and T. S. West, *J. Chem. Soc.*, 2743 (1958).

(3) C. V. Banks and D. T. Hooker, *Anal. Chem.*, **28**, 79 (1956).

(4) M. Murakami and Y. Yukawa, *Mem. Inst. Sci. Ind. Research Osaka Univ.*, **5**, 150 (1947); *Chem. Abstr.*, **47**, 2714 (1953).