The Identification of Sorbitol, 2-Desoxysorbitol and D-Mannitol in the Residual Sirup, Fraction D.—Fraction D was dehydrated by ethanol distillation under reduced pressure and a portion of this (7 g.) was acetylated with acetic anhydride and pyridine. The product obtained was fractionated from ether–petroleum ether (30–60°) and produced three fractions of crystalline material: (1) 4.5 g., m. p. 98–100°, $[\alpha]^{25}D$ +9.8° (*c* 5, chloroform), mixed melting point with a pure specimen of sorbitol hexaacetate (m. p. 99–100°) unchanged; (2) 2.3 g., m. p. 85–87°, $[\alpha]^{25}D$ +34.5° (*c* 5, chloroform), mixed melting point with a pure specimen of 2-desoxysorbitol pentaacetate (m. p. 86–87°) unchanged; (3) 0.2 g., m. p. 122–124°, $[\alpha]^{25}D$ +23.6° (*c* 5, chloroform), mixed melting point with a pure specimen of D-mannitol hexaacetate (m. p. 124–125°) unchanged.

Summary

1. Crystalline 2-desoxysorbitol has been obtained in approximately 5% yield from a commercial sorbitol-rich product manufactured by the electro-reduction of D-glucose at *p*H 7–10.

2. Crystalline D-mannitol has been isolated in approximately 1% yield from the same source.

3. The results of 1 and 2 are in harmony with an enolic mechanism of sugar interconversion under reducing conditions.

4. 2-Desoxysorbitol forms a monopyridine addition compound which, in the pure state, is quite insoluble in pyridine.

5. The crystalline pentaacetate, pentabenzoate, and di-*m*-nitrobenzylidene derivatives of 2-desoxysorbitol have been synthesized and characterized.

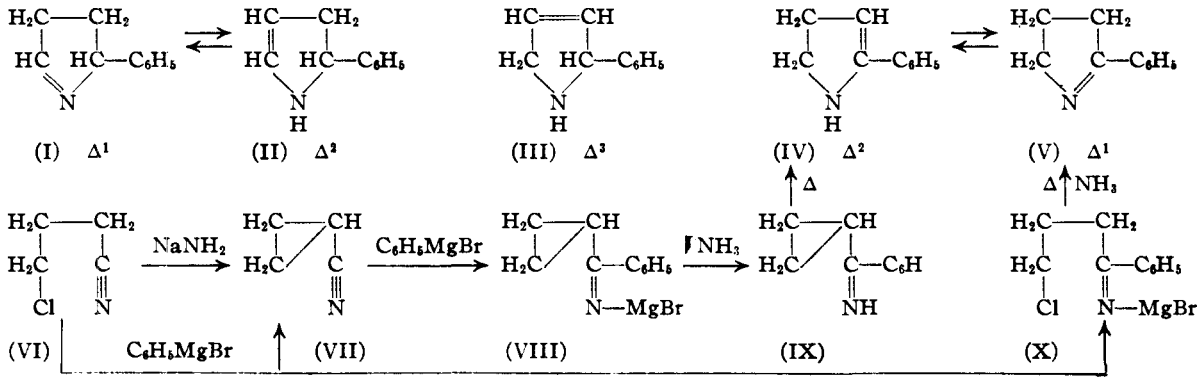
COLUMBUS, OHIO RECEIVED OCTOBER 17, 1945

[CONTRIBUTION FROM THE WALKER LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE]

The Synthesis of Δ^1-Pyrrolines[1]

BY JAMES V. MURRAY[2] AND JOHN B. CLOKE

Pyrroline Structure.—Five partial reduction products of 2-phenylpyrrole may be formulated as shown in structures (I)–(V). 2-Phenyl-Δ^3-pyrroline (III), whose structure involves no special problems, was described by Wohl.[3] 2-Phenyl-Δ^2-pyrroline (IV) was reported by Gabriel and Coleman,[4] and recently 5-phenyl-Δ^2-pyrroline (II) was announced by Gitsels and Wibaut.[5] Most workers on pyrrolines, *e. g.*, Mascarelli and Testoni,[6] have been reluctant to formulate such pyrrolines as those of Gabriel and Coleman and of Gitsels and Wibaut as the Δ^1 form, namely, (V) and (I), respectively. In this connection, Taylor and Baker[7] write, "Δ^1-Pyrrolines are unknown as individuals; they are possibly tautomeric with the Δ^2-pyrrolines." This tautomerism in the case of 2-phenylpyrroline (IV ⇆ V) was also suggested by one of us[8] in view of the fact that one of our syntheses suggested the Δ^1 and another the Δ^2 structure.



In our first synthesis of 2-phenylpyrroline, phenylmagnesium bromide was allowed to react with γ-chlorobutyronitrile (VI). Although this reaction may proceed along several paths,[9] the main product is the N-bromomagnesium derivative of phenyl γ-chloropropyl ketimine (X), which will give the pyrroline by ammonolysis,[8] careful hydrolysis[8] or pyrolysis, *e. g.*, in xylene.[10] If we ignore the possible tautomerism of the intermediates, the foregoing synthesis indicates the Δ^1 structure (V). In our second synthesis, the 2-phenylpyrroline was obtained by the pyrolytic rearrangement of phenyl cyclopropyl ketimine (IX), which was obtained from (VI) *via* (VII) and

(1) Based on the first part of a thesis presented by James V. Murray, Jr., to R. P. I. in June, 1934, for the degree of Chemical Engineer.

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(3) Wohl, *Ber.*, **34**, 1922 (1901).

(4) Gabriel and Colman, *ibid.*, **41**, 513 (1908).

(5) Gitsels and Wibaut, *Rec. trav. chim.*, **60**, 50 (1941).

(6) Mascarelli and Testoni, *Gass. chim. ital.*, **33**, 312 (1903).

(7) Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 491.

(8) Cloke, THIS JOURNAL, **51**, 1174 (1929).

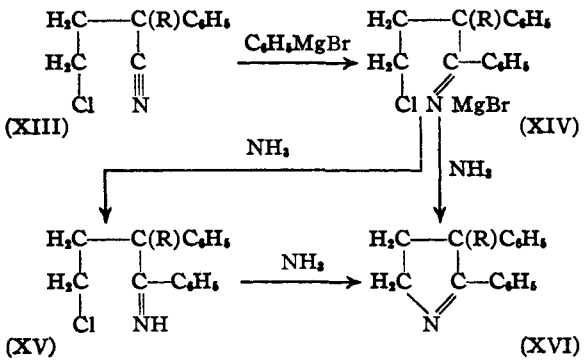
(9) Cloke, Baer, Robbins and Smith, *ibid.*, **67**, 2155 (1945).

(10) Craig, Bulbrook and Hixon, *ibid.*, **53**, 1831 (1931).

(VIII) as shown in the flow sheet. Although this synthesis appears to be more in harmony with the conventional Δ^2 structure, it does not exclude the Δ^1 form.

Synthesis of Δ^1-Pyrrolines.—The present paper describes the application of the γ-halobutyronitrile–Grignard–ammonolysis method to the synthesis of pyrrolines, which we believe to possess the Δ^1 structure. In order to establish the pyrroline double bond in the Δ^1 position, it was necessary to begin with a γ-halobutyronitrile wherein there was no mobile hydrogen atom on the α-carbon. With this problem in mind, a series of γ-chloro-α-alkyl-α-phenylbutyronitriles was synthesized several years ago[11] by the successive alkylation of phenylacetonitrile, $C_6H_5CH_2CN$ (XI) first with a suitable alkyl halide or sulfate to give an alkylphenylacetonitrile, C_6H_5CHRCN (XII), which was then transformed into the γ-chloro-α-alkyl-α-phenylbutyronitrile, $ClCH_2CH_2C(C_6H_5)(R)CN$ (XIII) by the use of sodium amide and ethylene chloride. The present paper describes an improvement on the original method to give definitely better yields.

For the synthesis of the Δ^1-pyrrolines, the proper γ-chloro-α-alkyl-α-phenylbutyronitrile (XIII) was allowed to react with an excess of phenyl magnesium bromide to give the corresponding N-bromomagnesium ketimine derivative (XIV). The ammonolysis of the reaction product gave the substituted pyrroline (XVI), either directly or through the stage of the ketimine (XV), or both



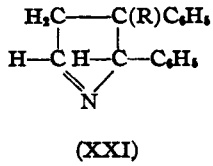
R = CH_3 (XVII); C_2H_5 (XVIII); n-C_3H_7 (XIX); n-C_5H_9 (XX)

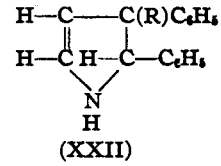
In some earlier work in this Laboratory, Krebs[12] attempted a similar synthesis, but instead of decomposing the addition product (XIV) in liquid ammonia, it was heated in xylene,[10] and subsequently in tetralin. From the former medium Krebs could obtain no pyrroline, while from the latter he isolated a small amount of a chloroplatinate which was shown by the present work to be identical with that derived from 2,3-diphenyl-3-methyl-Δ^1-pyrroline (XVII). In any event, ring closure by heating appears to be inferior to the liquid ammonia method.

(11) Hastings and Cloke, THIS JOURNAL, **56**, 2136 (1934).

(12) Henry G. Krebs, "Thesis," R. P. I., 1933.

The foregoing method of synthesis of our pyrrolines (XVII–XX) should establish the Δ^1-structure (XVI) unless this can isomerize to give (XXI), which might then give (XXII)





That this possibility must be considered follows from the fact that a Δ^1-pyrroline contains the same fundamental grouping as that present in the "methylene-azomethine" system, (XXIII) >CH—N=C< ⇄ >C=N—CH< (XXIV), of Ingold and Shoppee,[13] who have found that structures (XXIII) and (XXIV), especially if terminated at both ends by phenyl groups, will undergo prototropic isomerization in the presence of ethoxide ion in alcohol at 85°. However, *p*-methoxybenzylidenebenzylamine, $CH_3OC_6H_4CH=N—CH_2C_6H_5$, did not isomerize when boiled for a half hour with 2 *N* sulfuric acid. Prior to these studies, Sommelet had reported the isomerization of methylenebenzylamine to benzylidenemethylamine.[14] Since our pyrrolines were prepared under less drastic experimental conditions than those employed in the foregoing work, it seems probable that they would not undergo the same type of prototropic isomerization, although we expect to investigate this possibility as soon as time permits. All work done to date[15] supports the Δ^1 structure. No effort has been made to resolve the pyrrolines into their optically isomeric forms.

Experimental

Preparation of α-Phenylbutyronitrile.—The α-phenylbutyronitrile was prepared by the following modification of the procedure described by Hastings and Cloke.[11] The α-phenylpropionitrile, α-phenyl-*n*-valeronitrile and α-phenyl-*n*-capronitrile were made similarly.

A suspension of 78 g. (2 moles) of sodium amide in 1.5 liters of liquid ammonia was prepared in the usual manner[16] in a three-liter, three-necked, round-bottom flask fitted with a dropping funnel, a reflux condenser provided with a lime tower and a mechanical stirrer which operated through a mercury seal. As ammonia was allowed to evaporate, 1.5 liters of anhydrous benzene was added to the stirred mixture. When all of the ammonia had evaporated, the suspension of sodium amide was cooled in an ice-bath, and 236 g. (2 moles) of freshly distilled phenylacetonitrile was added slowly over the course of three and a half hours. An additional 500 ml. of dry benzene was added, and the mixture was stirred for two hours.

At this point 272 g. (2.5 moles) of dry ethyl bromide was added very slowly (six hours) to the well cooled sodium phenylacetonitrile suspension. The mixture was allowed to stand overnight, while the cooling bath gradually came to room temperature, and then refluxed on the steam-bath for three hours.

(13) Ingold and Shoppee, *J. Chem. Soc.*, 1199 (1929); Shoppee, *ibid.*, 968 (1930); 1225 (1931); 696 (1932).

(14) Sommelet, *Compt. rend.*, **157**, 853 (1913); Graymore and Davies, *J. Chem. Soc.*, 293 (1945).

(15) Magnuity, "Theses," R. P. I. (1941–1942); Murray, unpublished work (1938–1941).

(16) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934); Murray and Cloke, *ibid.*, **58**, 2016 (1936).

TABLE I

β-Alkyl-α,β-diphenyl-Δ¹-pyrroline	M. p.,[a] °C.	Yield, %	Formula	Mol. wt., Calcd.	Mol. wt., Found	Microanalyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Methyl (XVII)	55.2–55.5	78	$C_{17}H_{17}N$	235.1	228	86.81	86.70	7.28	7.28	5.95	6.05
					231		86.76		7.36		5.98
Ethyl (XVIII)	62.4–62.7	70	$C_{18}H_{19}N$	249.2	243	86.70	86.75	7.70	7.72	5.62	5.55
					239		86.66		7.75		5.70
n-Propyl (XIX)	45.0–46.0	58	$C_{19}H_{21}N$							5.32	5.43
											5.38
n-Butyl (XX)	Semi-solid	35	$C_{20}H_{23}N$							5.05	5.19
											5.28

[a] All melting points were determined on a heated microscope stage.

The suspension was treated with water, and the aqueous layer was drawn off. The benzene solution, after drying over calcium sulfate, was freed of solvent by distillation, the residue distilled under diminished pressure, and the fraction boiling 88–93° at 5 mm. was collected. This cut weighed 252 g. No effort was made to separate the α-phenylbutyronitrile from any unchanged phenylacetonitrile or α-ethyl-α-phenylbutyronitrile, since the rectification of this mixture is impractical, and no difficulty was encountered when this fraction was used in the second alkylation.

Preparation of γ-Chloro-α-ethyl-α-phenylbutyronitrile.—The γ-chloro-α-ethyl-α-phenylbutyronitrile was prepared by a modification of the method reported by Hastings and Cloke.[11] The corresponding α-methyl, α-*n*-propyl and α-*n*-butyl derivatives were prepared analogously.

Using the previously described apparatus and procedure, a suspension of 70.5 g. (1.8 moles) of sodium amide in 1.2 liters of dry benzene was prepared. A weight of 252 g. (1.74 moles) of the crude α-phenylbutyronitrile was added to the cooled sodium amide suspension over the course of four hours. The mixture was warmed for two hours on the steam-bath, when the flask was cooled in an ice bath, and 300 g. (3 moles) of ethylene chloride was added over a period of one-half hour. The reaction mass was stirred overnight, while the cooling bath attained room temperature, and then refluxed for five hours. The mixture was extracted with water, and the benzene solution dried over calcium sulfate. The benzene was removed by distillation, the residue distilled from a Claisen flask, and the portion boiling up to 121° at 3 mm. collected (305 g.). This material was fractionated through a 60-cm. Vigreux column, and the portion boiling from 105.0 to 106.0° at 1.5 mm. was collected (172 g.). Redistillation of the lower boiling cuts gave an additional 48 g. of product. The total make was 220 g. corresponding to a 53% yield based on the starting quantity of phenylacetonitrile.

Anal. (micro-Carius). Calcd. for $C_{12}H_{13}NCl$: Cl, 17.1. Found: Cl, 17.2, 17.3.

Preparation of 2,3-Diphenyl-3-ethyl-Δ¹-pyrroline (XVIII).—The usual apparatus for Grignard reactions was assembled. A weight of 7.3 g. (0.3 atom) of dry magnesium, and 50 g. (0.32 mole) of bromobenzene was converted to phenylmagnesium bromide in the presence of 250 ml. of anhydrous ether. At this point, 20.8 g. (0.1 mole) of γ-chloro-α-ethyl-α-phenylbutyronitrile in an equal volume of dry ether was added slowly to the phenylmagnesium bromide. This led to a mild refluxing of the ether, which was continued for eight hours.

The homogeneous solution was transferred to a separatory funnel and cautiously added to 500 ml. of liquid ammonia in a Dewar flask.[17] The Dewar flask was fitted with a long lime tower, and the mixture was allowed to stand, with occasional shaking, until all of the ammonia had evaporated (twenty-four hours).

The mixture was filtered, and the residue on the filter was washed five times with ordinary ether. The ether was distilled, and the residue was made strongly acid with 1:1 hydrochloric acid. The mixture was steam distilled, and the residual acid solution in the still pot was extracted successively with 50-ml. portions of carbon tetrachloride until no further color was removed. The aqueous solution was boiled with 2 g. of "Norit," filtered, the filtrate cooled in ice and then made alkaline with 10% sodium hydroxide. The white precipitate so obtained was usually semi-solid. With the exception of (XX), all of the pyrrolines could be obtained in a crystalline form by dissolving them in 100 cc. of 95% alcohol followed by precipitation by rapid stirring after the addition of two or three ice cubes, giving a white gummy material. Vigorous scratching and stirring resulted in rapid crystallization. This procedure was the most effective one tried. The high solubility of these pyrrolines in most solvents precluded the use of orthodox recrystallization procedures. The dry pyrrolines were stored in a vacuum desiccator over phosphorus pentoxide. After standing for six months they changed to a yellow resinous mass from which only traces of the original pyrroline could be recovered.

The pyrrolines listed in Table I were prepared from the corresponding γ-chloro-α-alkyl-α-phenylbutyronitrile by the foregoing procedure.

Δ¹-Pyrrolinium Picrates.—A solution of 0.2 g. of the pyrroline in glacial acetic acid was treated with one consisting of 0.2 g. of picric acid in hot glacial acetic acid. After boiling for a few minutes, water was added to the cooled solution until it became cloudy. Upon slight warming the picrate crystallized. It was purified by recrystallization from the minimum quantity of boiling acetic acid.

TABLE II

Picrate from	M. p., °C.
XVII	146.5–147.5
XVIII	131.0–131.7
XIX	151.1–151.4
XX	144.0–144.6

Δ¹-Pyrrolinium Chloroplatinates.—The pyrrolinium chloroplatinates were prepared in the usual manner from the pyrrolinium chlorides and aqueous 10% chloroplatinic acid.

TABLE III

Chloroplatinate of	M. p., °C. dec.	Formula	Microanalyses, Pt % Calcd.	Found
XVII	188	$C_{34}H_{36}N_2PtCl_6$	22.19	22.29, 22.33
XVIII	155	$C_{36}H_{40}N_2PtCl_6$	21.50	21.62, 21.55
XIX	216	$C_{38}H_{44}N_2PtCl_6$	20.86	20.90, 20.73
XX	193	$C_{40}H_{48}N_2PtCl_6$	20.25	20.30, 20.51

Δ¹-Pyrrolinium Chlorides.—The pyrrolinium chlorides were prepared by treating an ether solution of the base with a solution of hydrogen chloride in dry ether. An excess of hydrogen chloride gave resinous materials. The chlorides are not desirable derivatives, since they are extremely hygroscopic.

(17) This method is attended by some difficulty due to the precipitation of magnesium salt at the funnel tip. The reverse procedure is, however, not recommended in view of the hazard involved.

Summary

1. Improved procedures for the preparation of α-alkylphenylacetonitriles and γ-chloro-α-alkyl-α-phenylbutyronitriles have been developed.

2. Four new pyrrolines have been prepared by the action of phenylmagnesium bromide on the γ-chloro-α-alkyl-α-phenylbutyronitriles. The alkyl substituents used were methyl, ethyl, *n*-propyl and *n*-butyl. The chloroplatinates and picrates derived from the pyrrolines have been reported.

3. The method of synthesis of these pyrrolines points to the Δ^1 structure. The free pyrrolines resinify upon standing, a property which has been attributed to the Δ^2-pyrrolines by some writers.

TROY, N. Y. RECEIVED SEPTEMBER 28, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Quinolines. I. The Synthesis of 3-Methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinoline and Some 6-Substituted Derivatives

BY EDGAR A. STECK, LOUIS L. HALLOCK AND ARNOLD J. HOLLAND[1]

There has been considerable interest in 6-substituted quinolines because of the importance of the 6-methoxy group in the activity of quinine and pamaquin.[1a] The investigation of various 6-substituted quinolines has been of considerable scope since the synthesis of pamaquin, and many modifications of the nucleus and side-chain have been studied in attempts to increase the activity and lower the toxicity. Despite the great amount of information on 6-substituted quinolines having a basic chain attached to the 8-position, the study of the corresponding 4-dialkylaminoalkylamino types has received rather little attention.[2-10] The findings of the Russian investigators[2,3] have indicated clearly that the curative properties of the nucleus are not destroyed when the side-chain is attached at position 4, and also have shown that the compounds of this type no longer possess the gametocidal or gametostatic action of pamaquin, but, rather, a schizontocidal action in the manner of quinine and quinacrine. This latter observation apparently led to the interest of Gilman and Spatz[8] in the quinoline compounds which may be considered as "open models" of quinacrine, *viz.*, 6-methoxy-2-(3'-chlorophenyl)-4-(1'-methyl-4'-diethylaminobutylamino)-quinoline and related types.

Despite the indications of the work of Strukov,[2,3] Holcomb and Hamilton[7] and Van Arendonk and Shonle[9] have shown interest in 4-substituted 2-methylquinolines. The unpublished work of Strukov (1932) referred to by Magidson and by Gal'perin was upon three 2-methyl-6-methoxyquinolines having dialkylaminoalkylamino groups in position 4: *viz.*, the 4-diethylaminobutylamino, the 3-diethylamino-2-hydroxypropylamino and the 3-diethylaminopropylamino side-chains. There is essentially no information concerning the activity of analogous compounds having the methyl group in position 3, other than two patents,[4,5] which have been issued on certain compounds having a substituent in that position. The patents state that the compounds are effective against blood parasites, particularly plasmodia. The present contribution represents the first of a series dealing with the synthesis of 4-dialkylaminoalkylaminoquinolines carrying an alkyl group in position 3 and one or more substituents in the benzene ring. The compounds herein reported are all 3-methyl-4-(1'-methyl-4'-diethylaminobutylamino)-quinolines with hydrogen or a substituent (chloro, bromo, methoxy, ethoxy, or methyl) in position 6.

The method employed in the synthesis of the desired compounds is based upon the procedure of Conrad and Limpach[11,12] for the formation of 4-hydroxyquinoline derivatives from anilines and β-keto esters. Indication of the use of ethyl ethoxalylpropionate in the preparation of the 3-R (where R is CH_3) quinolines is given in the patents[4,5] mentioned above. No details are given for the procedure in either of the patents, hence it will be discussed in detail. As indicated by the equations, the aniline (I) and ethyl ethoxalylpropionate (II) are caused to react, and the product (III) is then readily cyclized at 250–260° to the quinoline ester, IV. The yields in both reactions are good, the first being 80% or better, and in the second the yields exceed 90%. Hydrolysis of the ester, IV, by aqueous sodium hydroxide, leads to nearly quantitative yields of the corresponding acid, V. The decarboxylation of V is most effectively carried out in mineral

(1) Present address: University of Minnesota, Minneapolis, Minn.

(1a) von Oettingen, "The Therapeutic Agents of the Quinoline Group," Chemical Catalog Co., New York, N. Y., 1933.

(2) Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937).

(3) Gal'perin, *Med. Parasitol. Parasitic Diseases* (*USSR*), **9**, No. 1-2, 44 (1940).

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970; *C. A.*, **35**, 3771[7] (1941).

(5) Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973[8] (1942).

(6) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(7) Holcomb and Hamilton, THIS JOURNAL, **64**, 1310 (1942).

(8) Gilman and Spatz, *ibid.*, **66**, 621 (1944).

(9) Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).

(10) Schulemann, Schönhöfer and Wingler, U. S. Patent 1,747,531; *C. A.*, **24**, 1705[9] (1930).

(11) Conrad and Limpach, *Ber.*, **20**, 944 (1887).

(12) Limpach, *ibid.*, **64**, 969 (1931).