[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY, STANFORD UNIVERSITY, AND THE WHITMORE LABORATORY, THE PENNSYLVANIA STATE COLLEGE]

The Synthesis of Dihydroniquidine

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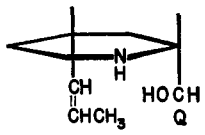
Both the dextro and levo forms of dihydroniquidine, a product from the alkaloid, quinidine, have been synthesized from primary starting materials. This completes the proof of structure for this substance as postulated on the basis of degradative studies by Gibbs and Henry.[3]

The structure of niquidine (I), a modification product of the alkaloid quinidine (III) has been proposed by Gibbs and Henry[3] on the basis of brilliant and convincing degradative studies. Ni-



I Niquidine[4]

quidine is readily converted into dihydroniquidine (II) by hydrogenation.

T. S. Work has published a series of three papers[5] on the synthesis of compounds related to niquidine and has reported the synthesis in small yield of a racemate which was not resolved and which was designated dihydro-x-niquidine.

We have now completed a total synthesis of dihydroniquidine in both *d*- and *l*-forms, the former of which was proven identical with the product from the naturally occurring alkaloid. The method employed depended upon a ready source of the appropriate ester, ethyl ϵ-benzoylamino-γ-*n*-propylcaproate (XIV) for reaction with ethyl quininate (XV) in a Claisen ester condensation according to the classical method first used by Rabe[6a] in his synthesis of dihydroquinidine and elaborated by subsequent investigators.[6b,6c] This is actually one of the methods explored by Work[5] and abandoned as showing little promise.

Work prepared the ϵ-benzoylamino-γ-*n*-propylcaproate ester by a four step process beginning with 4-*n*-propylpiperidine. We prepared this compound very conveniently in good yield from anethole by the scheme outlined below. The key to the synthesis was the Beckmann rearrangement which permitted the formation of the substituted caproic ester with the *n*-propyl group correctly situated in that portion of the molecule later to become the piperidine moiety of the dihydroniquidine structure. Ethyl quininate (XV) was then condensed with the caproate ester, XIV, in the presence of sodium hydride and the hydrolysis, decarboxylation, bromination, ring closure, and reduction were done by previously known procedures.[6] Theoretically the product could be a mixture of four racemates corresponding to niquidine, epi-C[9]-niquidine, niquine and epi-C[9]-niquine. Only one crystalline racemate was isolated.[7] This was separated as the monohydrochloride, m.p. 238–240°, and converted to the base (monohydrate), m.p. 101.0–101.5°. Work[5] reported the melting point of his dihydro-x-niquidine monohydrate as 98–100°.

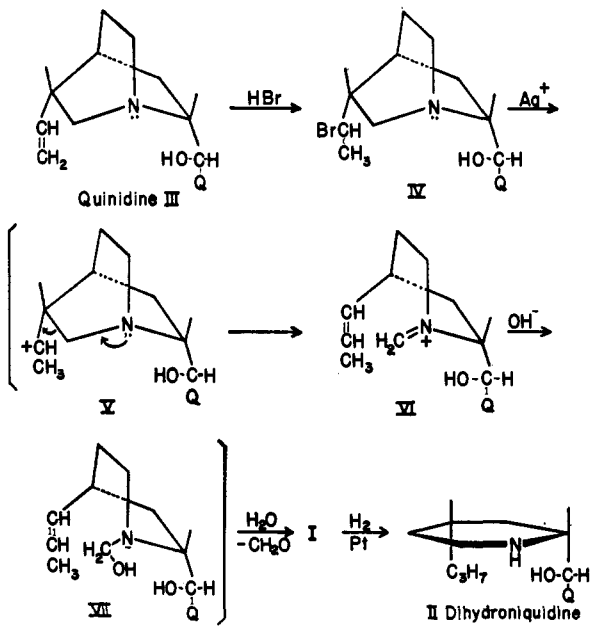
The base was resolved by treating with *l*-malic

(1) Parke, Davis and Co. Research Fellow, The Pennsylvania State College, 1946–1947.

(2) Parke, Davis and Co. Research Fellow, 1951, Stanford University.

(3) E. M. Gibbs and T. A. Henry, *J. Chem. Soc.*, 240 1294 (1939).

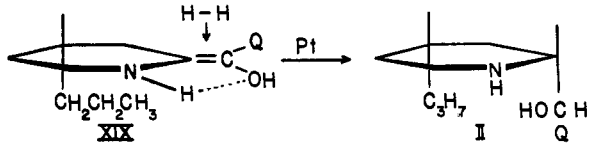
(4) This formula is based on the configurational studies of Prelog and Zalan (*Helv. Chim. Acta*, **27**, 535, 545 (1944)) and Prelog and Häfliger (*ibid.*, **33**, 2021 (1950)) and follows the Fischer convention; Q represents the 6-methoxy-4-quinolyl radical. The conversion of quinidine into niquidine may be represented in the light of modern electronic theory as follows.



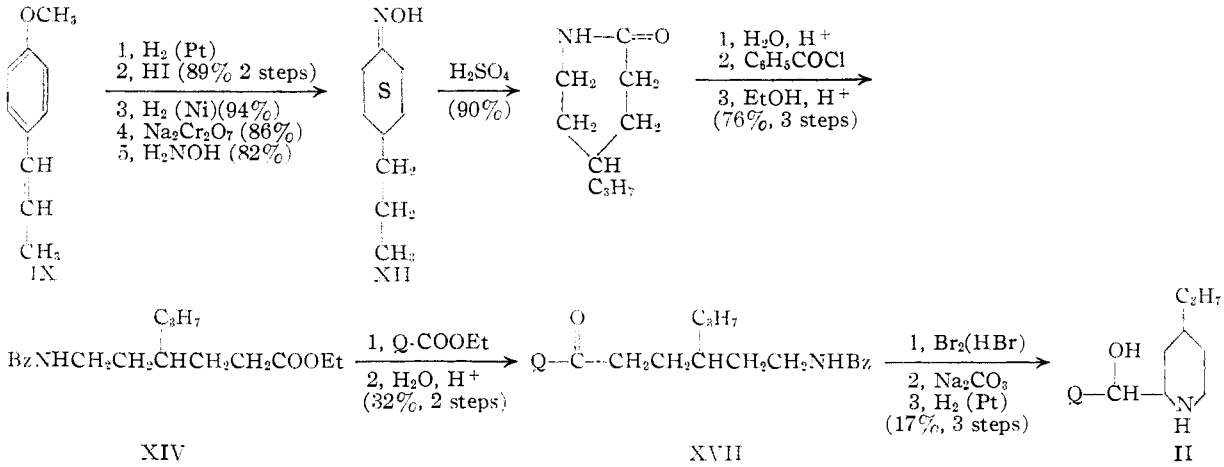
(5) T. S. Work, *J. Chem. Soc.*, 194, 197 (1946); 222 (1947).

(6) (a) P. Rabe and A. Schultze, *Ber.*, **66**, 120 (1933), and the many preceding papers in the series; (b) A. D. Ainley and H. King, *Proc. Roy. Soc. (London)*, **B125**, 60 (1938); (c) H. Sargent, THIS JOURNAL, **68**, 2688 (1946).

(7) We have speculated that, in the final step, reduction (in basic solution) takes place *via* the enol form which has the constellation depicted in XIX. The oxygen atom has been placed on the front edge



of the plane of the ring because of the possibility of hydrogen bonding between the ring nitrogen atom and the oxygen. When such a molecule approaches the surface of a hydrogen rich catalyst, it is logical to assume that the side opposite the bulky propyl group would offer freer access to the double bond. According to such considerations, one racemate, II, should predominate; this is *dl*-dihydroniquidine on the basis of Prelog's postulated relative configurations in the field of cinchona alkaloids.



IX XII XIV XVII II

acid.[8] A single crystallization gave a malate, m.p. 174°, which on decomposition with sodium hydroxide gave (+)-dihydroniquidine, m.p. 161.0–161.5°, $[\alpha]^{25}D$ +231.5 ± 1.0° (*c* 7, 0.1 *N* H_2SO_4) which was identical with a sample of dihydroniquidine prepared from quinidine with respect to specific rotation, melting point and mixture melting point of the base and the malate, as well as ultraviolet and infrared absorption spectra. The mother liquors from the resolution gave the previously unknown (−)dihydroniquidine. This, on crystallization with an equal weight of the (+)-dihydroniquidine obtained from the naturally occurring alkaloid, gave a product whose melting point was undepressed when mixed with a sample of the entirely synthetic racemate.

Acknowledgment.—We wish to thank Parke, Davis and Company for fellowship support which made this work possible.

Experimental[9]

Ethyl Quininate (XV).—This was prepared by the method of Thielepape and Fulde.[10] The use of sodium hydride and a few drops of absolute ethanol as the condensing reagent in the reaction of ethyl oxalate with N-methyl-N-aceto-*p*-anidisine to give 1-methyl-4-carbethoxy-6-methoxy-2-quinolone resulted in an improvement of the yield (reported 45%) to 70%.

***p*-*n*-Propylphenol (X).**[11]—Anethole (197 g., 1.3 moles) was reduced in a liter hydrogenation bottle in the presence of 1 g. of Adams catalyst with hydrogen at 3 atmospheres pressure and 100° in the absence of solvent. The resulting *p*-*n*-propylanisole was added to a cold mixture of acetic anhydride (1400 ml.) and hydriodic acid (700 ml., sp. gr. 1.50) and the mixture refluxed until the color turned from dark to pale yellow; most of the acetic acid and anhydride was distilled and the residue diluted with water and made basic with sodium hydroxide. The basic solution was extracted with ether and the extracts were discarded. The aqueous layer was acidified with hydrochloric acid, the *p*-*n*-propylphenol layer separated, and the aqueous layer extracted with ether. The extracts were combined with the phenol layer, dried over sodium sulfate, and the ether evaporated to give a residue of crude *p*-*n*-propylphenol (163 g., 90%). Cleavage of this methyl ether with hydriodic acid and acetic anhydride was much more practical than the method of Prey using sodium and pyridine.[12]

***p*-*n*-Propylcyclohexanone Oxime (XVII).**—Sodium metal (0.27 g.) was added to *p*-*n*-propylphenol (322 g.) and the mixture reduced in the presence of Raney nickel catalyst (10 g.) at 150° and 150 p.s.i. hydrogen pressure. The theoretical amount of hydrogen was consumed in one hour. This crude 4-*n*-propylcyclohexanol[13] was oxidized using sodium dichromate according to the method outlined by Gauthier[13] whose yield of 86% of 4-*n*-propylcyclohexanone was confirmed. Crude 4-*n*-propylcyclohexanone (300 g.) and hydroxylamine hydrochloride (164 g.) were mixed and a solution of sodium carbonate (125 g.) in water (295 ml.) was added during three hours. After 200 ml. of the sodium carbonate solution was added, a mixture of 450 ml. of ethanol and 700 ml. of water was added to facilitate mixing. The oil layer was decanted one hour after the addition of the sodium carbonate solution was complete and the aqueous layer extracted with ether. The oil layer and ether extracts were dried over sodium sulfate and distilled to give 274 g. (82%), b.p. 110–115° (1 mm.); reported,[13] b.p. 135–40° (21 mm.).

Ethyl ε-Benzoylamino-γ-*n*-propylcaproate (XIV).[5]—The Beckmann rearrangement of the 4-*n*-propylcyclohexanone oxime was conducted as indicated for cyclohexanone oxime.[14] A total of 192 g. of oxime was rearranged in this manner. The solution was treated with Norit, filtered, cooled to 10°, and 272 g. of 50% potassium hydroxide added. To this basic solution was then added 190 g. of benzoyl chloride over a period of one hour; stirring was continued for six hours during which time sufficient base was added at intervals to keep the *p*H of the solution above 9. The solution was neutralized with hydrochloric acid to congo red endpoint and extracted twice with 700-ml. portions of ether. Distillation of the ether from the dried extracts gave 333.5 g. of crude ε-benzoylamino-γ-*n*-propylcaproic acid. This was directly esterified by refluxing with 700 ml. of absolute ethanol, 150 ml. of benzene and 5 ml. of concentrated sulfuric acid under a column so that the water–benzene azeotrope could be removed. The sulfuric acid was neutralized by adding the calculated amount of anhydrous sodium carbonate and the distillation continued until most of the excess alcohol and benzene was removed. The residue was taken up in ether and the extract washed first with 100 ml. of cold very dilute hydrochloric acid solution, followed by two 100-ml. portions of cold sodium carbonate solution. After the ether was removed from the dried solution on the steam-bath, a viscous red oil (305 g.) remained which distilled at 185–194° (0.015 mm.), $n^{20}D$ 1.5120, 270 g. (69%), reported by Work,[5] b.p. 214–216° (0.7 mm.).

Anal. Calcd. for $C_{18}H_{27}O_3N$: C, 70.78; H, 8.91; N, 4.59. Found: C, 70.68; H, 8.96; N, 5.24.

6-Methoxyquinolyl α-Bromo-γ-propyl-ε-amylamino Ketone Hydrobromide (XVIII).—Ethyl quininate (XV) (9.0 g., 0.039 mole) and ethyl ε-benzoylamino-γ-propylcaproate (XVI) (12.1 g., 0.039 mole) were dissolved in dry benzene

(8) A Referee has brought to our attention that D. R. Howton reported the use of malic acid as a resolving agent for quinine-type compounds at the 111th American Chemical Society Meeting, April, 1947.

(9) All melting points were uncorrected.

(10) E. Thielepape and A. Fulde, *Ber.*, **72**, 1432 (1939).

(11) H. Ungnade and A. Ludutsky, *J. Org. Chem.*, **10**, 520 (1945), have described the conversion of anethole to 4-*n*-propylcyclohexanone by reduction in the presence of Raney nickel to 1-methoxy-4-*n*-propylcyclohexane followed by demethylation and oxidation in an overall yield of 72%.

(12) V. Prey, *Ber.*, **76B**, 156 (1943).

(13) B. Gauthier, *Ann. chim.*, **20**, 612 (1945).

(14) J. C. Eck and C. S. Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 76.

and sodium hydride (1.4 g.) was added under an inert atmosphere. The mixture was warmed and stirred and a rapid evolution of hydrogen took place at about 70°; thereafter the temperature was maintained at 90° for 36 hours. To the stirred, cooled mixture were added 64 ml. of concentrated hydrochloric acid and 22 ml. of water. The resulting mixture was refluxed for 19 hours to hydrolyze and decarboxylate the product. After the solution was thoroughly cooled, ice was added and then 46 g. of sodium hydroxide, dissolved in 88 ml. of water. The liberated keto amine (XVII) was extracted as rapidly as possible, first with 25 ml. of chloroform and then with three 10-ml. portions of chloroform. The emulsion which formed was broken by centrifuging. These chloroform extracts were immediately poured with shaking into a flask containing 24 g. of 40% hydrobromic acid. The chloroform layer was extracted with an additional 10 g. of 40% hydrobromic acid solution and the gain in weight of the combined acid extracts (5.00 g., 32%) taken as the yield of the keto amine base (XVII). The extracts were diluted to give a 30% hydrogen bromide solution and brominated at 60° by passing a nitrogen stream carrying 2.1 g. of bromine into the well-stirred solution. It was essential that the rate of bromine addition did not exceed the rate of absorption. After the bromine was added, the temperature of the mixture was raised rapidly to 100° and then lowered immediately to 0°. The light tan solid (XVIII) which separated weighed 5.78 g. (26.6%), m.p. 188–191° after washing with cold absolute ethanol and drying. Recrystallization from methanol raised the melting point to 194–195°.

Anal. Calcd. for $C_{19}H_{25}O_2N_2Br\cdot 2HBr$: N, 5.05; total Br, 43.19; ionic Br, 28.78. Found: N, 4.81; total Br, 43.33, 43.12; ionic Br, 28.85, 28.72.

***dl*-Dihydroniquidine (VIII).**—Purified bromo ketone hydrobromide (XVIII) from above (2.3 g.) and platinum oxide catalyst (0.13 g.) were slurried with 21 ml. of ethanol, the flask swept with nitrogen, and a saturated sodium carbonate solution (10.8 ml.) added dropwise with stirring. After 1.5 hours, an additional 45 ml. of methanol was added, the mixture was warmed slightly to effect complete solution, and reduced by stirring with hydrogen at atmospheric pressure.[15] The reaction mixture was filtered, the methanol solution treated with Norit, and the filtrate rapidly evaporated to dryness at room temperature under reduced pressure. This residue was taken up in cold dilute hydrochloric acid and neutralized by slow addition of sodium carbonate solution. Several crops of the *dl*-dihydroniquidine monohydrochloride were obtained but all melted at approximately 230–235° dec., and so were combined and recrystallized from methanol to give 300 mg. (17%), m.p. 232–240° dec., depending upon rate of heating. Although the mother liquors were investigated, there was no indication of a second crystalline racemate being present in significant amounts.

Anal. Calcd. for $C_{19}H_{26}O_2N_2\cdot HCl$: C, 65.05; H, 7.76; Cl, 10.1. Found: C, 64.66, 64.69; H, 7.67, 7.74; Cl, 10.1.

Conversion to the base by solution of the monohydrochloride in dilute hydrochloric acid and pouring into cold 30% potassium hydroxide gave crystals which melted at 101–101.5° after crystallization from aqueous ethanol. The anhydrous material melts at 144–145°.

Anal. Calcd. for $C_{19}H_{26}O_2N_2\cdot H_2O$: C, 68.64; H, 8.48; H_2O, 5.42. Found: C, 68.70; H, 8.39; H_2O, 5.22.

Resolution of *dl*-Dihydroniquidine.—A solution of 150 mg. of *dl*-dihydroniquidine monohydrate in 2 ml. of 95% ethanol was mixed with a solution of 61 mg. of (−)-malic acid in 1 ml. of 95% ethanol and warmed. After eight hours at 2°, the crystals were filtered, washed with a little cold alcohol and dried to give 90 mg. of white crystals, m.p. 174–175°. A mixture of this with a sample of the malate prepared from dihydroniquidine obtained from the alkaloid by the method of Gibbs and Henry[3] gave an undepressed melting point. The malate (85 mg.) was dissolved in 2 ml. of 10% sulfuric acid to give a characteristic blue fluorescent solution from which the free base was obtained by adding to 30% potassium hydroxide solution. The precipitate was centrifuged, washed with water, and crystallized from warm alcohol to which water was added, 41.5 mg., m.p. 160–161°; recrystallization raised the melting point to 160.0–161.5°.

Anal. Calcd. for $C_{19}H_{26}O_2N_2$: C, 72.58; H, 8.32; N, 8.92. Found: C, 72.27; H, 8.31; N, 9.26.

The melting point of this sample when mixed with (+)-dihydroniquidine (m.p. 160–161°, lit. value[3] 165°) prepared from quinidine was 160–161°. The rotation $\alpha^{25}D$ +3.325 ±0.015° (*l* 2, *c* 0.717, 0.1 *N* H_2SO_4), $[\alpha]^{25}D$ +231.5 + 1.0° compares to the literature value[3] of $[\alpha]^{25}D$ +231.6°. The infrared absorption spectrum in Nujol paste was indistinguishable from that of a sample of dihydroniquidine prepared from the alkaloid. The ultraviolet absorption spectra were also identical. The previous unknown (−)-dihydroniquidine was obtained by evaporating the mother liquors from the crystallization of the (−)-malate-(+)-dihydroniquidine, taking the residue up in 10% sulfuric acid and precipitating the (−)-dihydroniquidine by adding it to 30% potassium hydroxide. The precipitate was washed with water and twice crystallized from aqueous ethanol to give 29.1 mg., m.p. 160–161.5°, $[\alpha]^{24.5}D$ −229.0 ± 2° (0.1 *N* H_2SO_4, *c* 0.58). A 1:1 mixture of this (−) isomer with a sample of the "natural" (+)-dihydroniquidine was crystallized from ethanol and the product found to melt at 99–100°. When these crystals were mixed with the synthetic racemate (m.p. 101.0–101.5°) a melting point of 100–101° was observed.

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(15) In another run it was found that the reduction proceeded much more rapidly by adding prereduced platinum oxide catalyst immediately after the neutralization.