NOTES

The Catalytic Hydrogenation of the Reissert Compound and Hydrolysis of the Product

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McEwen, et al.,[1] have reported that the Reissert compound, which is formulated as 1-benzoyl-2-cyano-1,2-dihydroquinoline (I), undergoes catalytic hydrogenation in alcoholic solution and in the presence of platinum oxide to give 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline (II); and, further, that acid hydrolysis of the latter gives benzaldehyde, albeit in smaller yield than does the Reissert compound.

The author has been engaged for some time on on the problem of the structure and mode of hydrolysis of I, and during that time has prepared model compounds related to I but in which the 3,4-double bond of structure I was deliberately omitted. The results obtained with these suggested that, in contrast to the conclusion of McEwen and his co-workers, compound II should undergo normal acid hydrolysis to give benzoic acid and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid.

Careful repetition of the hydrogenation of I under the conditions described by McEwen, et al.,[1] led to the isolation of a product with a somewhat indefinite melting point of 136–137°, becoming clear at 139–140°, after recrystallization from ethanol. This melting point is only two degrees higher than that reported by McEwen, et al.,[1] for compound II, prepared in the same manner. Analysis was in agreement for 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline. However recrystallization of our product from ethanol and from acetic acid raised the melting point to 144–146°, but had little effect upon the analysis figures which were still in agreement for compound II. Acid hydrolysis of this product (m.p. 144–146°) yielded only a 5.3% yield of benzaldehyde, (isolated as the 2,4-dinitrophenylhydrazone) but in addition some 1,2,3,4-tetrahydroquinoline-2-carboxylic acid (isolated as the 1-nitroso derivative) was obtained. This acid was thought to have arisen from compound II whereas the benzaldehyde was thought to have arisen from some of compound I also present in the hydrogenation product. A third compound must be present in the hydrogenation product in order to obtain an analysis completely in agreement for that required by compound II alone.

Crystallization of the initial hydrogenation product (m.p. 136–137°) from ethanol followed by repeated crystallization from benzene and petroleum ether (b.p. 80–100°) raised the melting point by

12°, to 148–149°. This purified product analyzed correctly for compound II and acid hydrolysis led to only 2.5% benzaldehyde (the yield was based only on the crude 2,4-dinitrophenylhydrazone and represents the maximum limit) but to 94% of 1,2,3,4-tetrahydroquinoline-2-carboxylic acid (isolated as the 1-nitroso derivative) and 65% of benzoic acid.

The production of benzoic acid and of 1,2,3,4-tetrahydroquinoline-2-carboxylic acid upon acid hydrolysis and in such high yield, accord completely with the formulation of the partial hydrogenation product, m.p. 148–149°, as the required 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline (II).

This work was confirmed finally in the synthesis of 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline by an independent and unambiguous route from methylquinaldinic ester. Hydrogenation of the quinoline nucleus had been described by Wieland, et al.,[2] yielding methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate. Benzoylation with benzoyl chloride in pyridine afforded methyl 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylate, which was converted smoothly to 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid by refluxing with aqueous methanolic potassium bicarbonate. This acid then was treated with sulfamide in pyridine to yield the amide derivative, using the method of Kirsanov and Zolotov.[3] The final conversion of 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxyamide into the required 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline (II) was carried out over phosphorus pentoxide in benzene in the presence of triethylamine, following the work of McElvain and Clarke,[4] and yielded a product, m.p. 149°, which was not depressed upon admixture with product C (m.p. 148–149°), isolated from the partial hydrogenation of the Reissert compound I.

Acid hydrolysis of the pure 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline (m.p. 149°) yielded benzoic acid and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, but no benzaldehyde could be detected either by its odor or as the 2,4-dinitrophenylhydrazone.

The complete synthesis of compound II by this route establishes its structure and since the Reissert compound I has now been shown to yield some of compound II (product C from the hydrogenation experiment) it would suggest that the structure given for compound I is, indeed, correctly assigned.

The isolation of different products from the acid hydrolysis of compounds I and II makes necessary a drastic revision of the mechanisms so far proposed for the acid hydrolysis of I to give benzaldehyde and quinoline-2-carboxylic acid. It would appear that an electronic displacement involving the 3,4-double bond is probably operative in this case. This

(1) W. E. McEwen, R. H. Terss and I. W. Elliott, This Journal, 74, 3605 (1952).

(2) H. Wieland, O. Hettche and T. Hoshino, Ber., 61, 2371 (1928).

(3) A. V. Kirsanov and Y. M. Zolotov, J. Gen. Chem., 19, 2201 (1949); C. A., 44, 4446 (1950).

(4) S. M. McElvain and R. L. Clarke, This Journal, 69, 2657 (1947).

may simply mean that aromatization to the quinoline nucleus supplies the energy for the Reissert reaction but the exact nature of the electronic displacements may be quite complex.

Experimental

Partial Hydrogenation of the Reissert Compound.—1-Benzoyl-2-cyano-1,2-dihydroquinoline (10 g., 0.038 mole) dissolved in ethanol (1,500 ml.) over platinum oxide (1 g.) was hydrogenated by the method of McEwen, et al.,[1] until one mole of hydrogen has been absorbed. The hydrogenation then was stopped mechanically. An independent experiment had shown that the graph of hydrogen absorption against time showed no break corresponding to this degree of hydrogenation. The catalyst then was filtered off and the solution concentrated to 150 ml., treated with charcoal, filtered, and the product A (6.15 g., m.p. 136–137°, becoming clear at 139–140°) allowed to crystallize out slowly. The m.p. was depressed to 130–133° upon admixture with the starting material.

Anal. Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.34; N, 10.68. Found: C, 78.05; H, 5.11; N, 10.62.

Some of this product A (2 g.) was recrystallized from acetic acid followed by ethanol and yielded a purer product B (1 g., m.p. 144–146°). The m.p. was again depressed to 130–133° upon admixture with the starting material.

Anal. Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.34; N, 10.68. Found: C, 78.15; H, 5.40; N, 10.75.

Recrystallization of another part of the product A (3.65 g.) many times from benzene and petroleum ether (b.p. 80–100°) resulted in the isolation of a highly crystalline pure white product C (1.2 g., m.p. 148–149°). This compound did not depress the m.p. of product B on admixture but like the other products A and B, depressed its m.p. when mixed with the starting Reissert compound to 130–133°. This product C proved to be the required 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline.

Anal. Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.34; N, 10.68. Found: C, 77.70; H, 5.30; N, 10.60.

Acid Hydrolysis of Product B.—The product B (0.5 g.) from the partial hydrogenation of the Reissert compound was refluxed for 1.25 hr. with a mixture of 12.5 ml. of concentrated hydrochloric acid and 12.5 ml. of water. Benzaldehyde could be detected by its odor and was isolated by the addition of 2,4-dinitrophenylhydrazine (0.5 g.) in sulfuric acid solution, as its 2,4-dinitrophenylhydrazone (0.03 g., m.p. 236–238°). The excess 2,4-dinitrophenylhydrazine was removed by adding an excess of acetone (1 ml.) and filtering off the precipitate. Subsequent treatment of the filtrate with excess sodium nitrite precipitated a product which soon solidified and was extracted with chloroform. The solvent was removed and the residue crystallized from ether and petroleum ether (b.p. 40–60°) to yield 0.03 g., m.p. 123–125° dec. This compound was shown to be 1-nitroso-1,2,3,4-tetrahydroquinoline-2-carboxylic acid.[2]

Anal. Calcd. for $C_{10}H_{10}O_3N_2$: C, 58.25; H, 4.85; N, 13.6. Found: C, 58.15; H, 4.90; N, 13.5.

Acid Hydrolysis of Product C.—The product C from the partial hydrogenation of the Reissert compound was hydrolyzed very carefully in order to isolate the maximum quantities of the products. The method adopted was based on the results of the earlier hydrolysis of product B. The product C (0.5 g.) was refluxed with 12.5 ml. of concentrated hydrochloric acid and 12.5 ml. of water for 1 hr. After cooling, the mixture was extracted with chloroform to remove any benzoic acid or benzaldehyde. The benzoic acid (0.15 g., m.p. 121–123°) was recovered by extraction with 2 N sodium hydroxide and acidification of the extract with concentrated hydrochloric acid. To the chloroform solution was then added 2,4-dinitrophenylhydrazine (0.5 g.) dissolved in acetic acid. After removal of the solvents, the residue was treated with an equal mixture of sulfuric acid and water. Only a cloudy solution remained containing insufficient material to collect. (Benzaldehyde was shown to be over 90% recoverable after refluxing with hydrochloric acid and being subjected to identical treatment. An independent experiment in which the product C (0.1 g.) was hydrolyzed as before but in the presence of 2,4-dinitrophenylhydrazine yielded only 0.0028 g. of the crude 2,4-dinitrophenylhydrazone of benzaldehyde). The original

acid hydrolysate, after chloroform extraction, then was treated with sodium nitrite and the 1-nitroso-1,2,3,4-tetrahydroquinoline-2-carboxylic acid[2] (0.37 g., m.p. 121–123° dec.) was recovered using chloroform to extract it as before. Recrystallization from benzene and petroleum ether (b.p. 40–60°) yielded the pure acid (0.3 g., m.p. 124–126° dec.) identical with the sample from the hydrolysis of product B. The acid mother liquors then were neutralized with sodium carbonate and then acidified with acetic acid. The addition of cupric sulfate to the buffered solution failed to yield any precipitate, thus showing the absence of any appreciable quantity of quinaldinic acid. Product C was shown therefore to be practically pure 1-benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline since it yielded mainly benzoic acid and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid upon acid hydrolysis.

Methyl 1,2,3,4-Tetrahydroquinoline-2-carboxylate.—Methylquinaldate (7.5 g., 0.0401 mole) in ethanol (150 ml.) over platinum oxide (0.5 g.) was hydrogenated by the method of Wieland, et al.,[2] until two molecules of hydrogen had been absorbed. The catalyst was removed and the solution concentrated in vacuo. The residual oil was distilled yielding methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate [6.9 g., b.p. 106–110° (0.05 mm.)].

Methyl 1-Benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylate.—Methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (6.9 g., 0.0362 mole) in dry pyridine (30 ml.) was treated dropwise with benzoyl chloride (5.5 ml., 0.0473 mole) whilst the mixture was stirred and the temperature controlled between 0–10°. Ten minutes after the addition, the mixture was allowed to reach room temperature and then set aside for 24 hr. The mixture was poured onto ice and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate, water, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed and the residue triturated with petroleum ether (b.p. 40–60°) until a solid appeared. The methyl 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (8.5 g., m.p. 108–110°) was collected and recrystallized from methanol to yield the pure product (7 g., m.p. 111–112°).

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.2; H, 5.76; N, 4.75. Found: C, 73.3; H, 5.71; N, 4.78.

1-Benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid.—Methyl 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (1.5 g., 0.0051 mole) was dissolved in methanol (35 ml.) and a solution of potassium bicarbonate (0.5 g., 0.0050 mole) in water (7 ml.) was added. A precipitate appeared and was taken up by the addition of just sufficient water to obtain complete solution. The solution was refluxed for 2.25 hr. The solvent was removed and water added to the residue. A small quantity of oil remained but it soon solidified and was filtered off. It was shown to be some unchanged ester (0.2 g., m.p. 109–110°). The aqueous filtrate was acidified with concentrated hydrochloric acid and 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (1.1 g., m.p. 180–183°) was filtered off and recrystallized from ethanol to yield the pure product (1 g., m.p. 184–186°).

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.6; H, 5.34; N, 5.0. Found: C, 72.8; H, 5.49; N, 5.1.

1-Benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxyamide.—1-Benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (1.5 g., 0.0054 mole) and sulfamide (1.1 g., 0.0115 mole) were dissolved in pyridine (5 moles) and heated at 100° for 3 hr. The pyridine was removed in vacuo, the residue treated with water and the mixture extracted with chloroform. The extract was washed with water, potassium bicarbonate solution, again with water and then dried over magnesium sulfate (anhydrous). Acidification of the potassium bicarbonate solution failed to yield any unchanged acid. The chloroform solution was concentrated and the residue triturated with petroleum ether (b.p. 40–60°). The solid (1.4 g., m.p. 180° but softening from 150°) was collected and recrystallized from ethyl acetate and petroleum ether (b.p. 40–60°) yielding the pure 1-benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxyamide (0.8 g., m.p. 188–189°). The m.p. was depressed to 170–174° upon admixture with the original acid.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.9; H, 5.72; N, 10.0. Found: C, 72.9; H, 6.00; N, 9.55.

1-Benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline.—1-Benzoyl-1,2,3,4-tetrahydroquinoline-2-carboxyamide (0.44 g., 0.0016 mole) and dry triethylamine (0.45 ml., 0.0032 mole)

in dry benzene (20 ml.) were treated when refluxing with phosphorus pentoxide (0.3 g., 0.0021 mole) and then refluxed for 1 hr. A further portion of phosphorus pentoxide (0.2 g., 0.0014 mole) then was added and the mixture refluxed for another 2 hr. The solvent was removed *in vacuo* and the residue solidified, washed with petroleum ether (b.p. 40-60°) and then dissolved in benzene and chromatographed over activated alumina (using benzene as the eluting solvent). The product, after removing the benzene, was recrystallized from benzene and petroleum ether (b.p. 60-80°) to yield the required 1-benzoyl-2-cyano-1,2,-3,4-tetrahydroquinoline (0.2 g., m.p. 149°). The m.p. was not depressed upon admixture with product C (m.p. 148-149°) obtained from the partial hydrogenation of the Reissert compound (I).

Anal. Calcd. for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.34; N, 10.68. Found: C, 77.90; H, 5.35; N, 10.50.

Acid Hydrolysis of Pure 1-Benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline.—1-Benzoyl-2-cyano-1,2,3,4-tetrahydroquinoline (0.1 g., 0.0004 mole), which had been synthesized from the amide, was refluxed for 1 hr. with concentrated hydrochloric acid (2.5 ml.) and water (2.5 ml.) containing 2,4-dinitrophenylhydrazine (0.1 g., 0.00055 mole). The solution remained completely clear and was treated with water (10 ml.) before cooling. The clear solution was poured into sodium bicarbonate (2.5 g.) in water (20 ml.) and filtered to remove the 2,4-dinitrophenylhydrazine. The alkaline solution was concentrated *in vacuo* to a small bulk (5 ml.) and acidified with concentrated hydrochloric acid. The precipitate was filtered off, after cooling, and recrystallized from water to yield benzoic acid (0.015 g., m.p. 122-123°).

The addition of excess sodium nitrite to the mother liquors gave an oily precipitate which was extracted with chloroform and the extract dried and concentrated. The solidified residue was recrystallized from benzene and petroleum ether (b.p. 40-60°) to yield 1-nitroso-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (0.03 g., m.p. 119-123° dec.).

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The Evaluation of the Kinetic Constants of Enzyme-Catalyzed Reactions by the Method of Foster and Niemann[1]

BY THOMAS H. APPLEWHITE AND CARL NIEMANN[2]

In a recent communication from these laboratories Foster and Niemann,[3,4] in extending an earlier treatment of Walker and Schmidt,[5] described a procedure for the graphical evaluation of the kinetic constants of enzyme catalyzed reactions whose rates, in so far as they are dependent upon the con-

(1) Supported in part by a grant from Eli Lilly and Co.

(2) To whom inquiries regarding this article should be sent.

(3) R. J. Foster and C. Niemann, *Proc. Natl. Acad. Sci.*, **39**, 999 (1953).

(4) Attention is called to three typographical errors in ref. 3: on p. 1000 the left hand member of equation 4 should read "$k_3[E]t$" instead of "$k_3[E]t$," on pp. 1000 and 1002 the equation describing the slopes of the ($[S]_0 - [S]_t$)/t *vs.* ($\ln[S]_0/[S]_t$)/t plots should read "$-K_S(K_P + [S]_0)/(K_P - K_S)$" instead of "$-K_S(K_P + [S]_0)/(K_S - K_P)$" and in Fig. 1, the slopes of the lines drawn through the hypothetical experimental points should read "$-K_S(K_P + [S]_0)/(K_P - K_S)$" instead of "$K_S(K_P + [S]_0)/(K_P - K_S)$."

(5) A. C. Walker and C. L. A. Schmidt, *Arch. Biochem.*, **5**, 445 (1944).

centration of enzyme and specific substrate, are described by equation 1

$$k_3[E]t = K_S\left(1 + [S]_0 \sum_{j=1}^{n} 1/K_{P_j}\right) \ln [S]_0/[S]_t + \left(1 - K_S \sum_{j=1}^{n} 1/K_{P_j}\right)([S]_0 - [S]_t) \quad (1)$$

This procedure, which was developed for the case where $\sum_{j=1}^{n} 1/K_{P_j} = 1/K_P$, is based upon the fact that in a plot of ($[S]_0 - [S]_t$)/t *vs.* ($\ln[S]_0/[S]_t$)/t lines of slope $[S]_0$ drawn through the origin will intersect those of slope $-K_S(K_P + [S]_0)/(K_P - K_S)$ at points which define, in terms of the ordinate ($[S]_0 - [S]_t$)/t, the corresponding initial velocities. As this fact was not clearly established, nor clearly stated, in the earlier communication[3] we shall in this communication offer proof of its validity.

If equation 1 for the case where $\sum_{j=1}^{n} 1/K_{P_j} = 1/K_P$ is transformed into the usual slope-intercept form one obtains equation 2

$$([S]_0 - [S]_t)/t = k_3[E]K_P/(K_P - K_S) - K_S(K_P + [S]_0)(\ln[S]_0/[S]_t)/t(K_P - K_S) \quad (2)$$

It will be seen from equation 2 that with a plot of ($[S]_0 - [S]_t$)/t *vs.* ($\ln[S]_0/[S]_t$)/t one will obtain, for various values of $[S]_0$ and t, a series of lines of slope $-K_S(K_P + [S]_0)/(K_P - K_S)$. For each of these lines there is a point corresponding to $t = 0$ and this point may be located by examination of the limits of the two parameters ($[S]_0 - [S]_t$)/t and ($\ln[S]_0/[S]_t$)/t as $t \to 0$. The limit of ($[S]_0 - [S]_t$)/t as $t \to 0$ is clearly $-d[S]/dt$ and that of ($\ln[S]_0/[S]_t$)/t as $t \to 0$ is ($-d[S]/dt$) (1/$[S]_0$). Therefore, for the condition that $t = 0$ lines of slope $[S]_0$ drawn through the origin of a ($[S]_0 - [S]_t$)/t *vs.* ($\ln[S]_0/[S]_t$)/t plot will intersect the lines of slope $-K_S(K_P + [S]_0)/(K_P - K_S)$ at points corresponding to $t = 0$. It is emphasized that the relation ($[S]_0 - [S]_t$)/$t = [S]_0(\ln[S]_0/[S]_t)/t$ defines a point for the condition that $t = 0$ and does not describe the relation between ($[S]_0 - [S]_t$)/t and ($\ln[S]_0/[S]_t$)/t for other values of t.

It has been noted above that the parameters of the points corresponding to $t = 0$, *i.e.*, the points of intersection of the lines of slope $[S]_0$ with those of slope $-K_S(K_P + [S]_0)/(K_P - K_S)$, are, respectively, $-d[S]/dt$ for the ordinate and ($-d[S]/dt$)· (1/$[S]_0$) for the abscissa. Since by definition $-d[S]/dt = v_0$ and ($-d[S]/dt$)(1/$[S]_0$) $= v_0/[S]_0$ it follows that a line drawn through the points of intersection corresponding to $t = 0$ for various values of $[S]_0$ will possess the same characteristics as one obtained by a plot of v_0 *vs.* $v_0/[S]_0$,[6] *i.e.*, will have a slope of $-K_S$, an ordinate intercept of $k_3[E]$ and an abscissa intercept of $k_3[E]/K_S$. That the initial velocities, *i.e.*, the values of v_0, are defined in terms of the ordinate, *i.e.*, ($[S]_0 - [S]_t$)/t, is evident when the terms in K_P in equation 2 are eliminated through the use of the relation ($[S]_0 - [S]_t$)/$t = [S]_0 (\ln[S]_0/[S]_t)/t$ to give equation 3 which is singular for the condition that $t = 0$.

$$([S]_0 - [S]_t)/t = k_3[E][S]_0/(K_S + [S]_0) = v_0 \quad (3)$$

(6) G. S. Eadie, *J. Biol. Chem.*, **146**, 85 (1942).