pyropseudaconine, a small quantity of a hitherto unobserved by-product.

5. The action of 10 N sulfuric acid on pseudaconine gave rise to des-O-methyldemethoxydehydropseudaconine.

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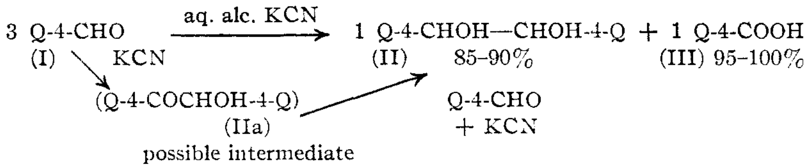
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Cinchoninaldehyde: Benzoin and Cannizzaro Reactions

BY ARTHUR P. PHILLIPS

In continuation of our studies with cinchoninaldehyde (I),[1] it has been found that this aldehyde exhibits an unexpected reaction with potassium cyanide. Instead of the usual benzoin type of product (IIa) the hydrobenzoin-type of compound (II) was obtained together with cinchoninic acid (III). The structure of II was established by oxidation with chromic anhydride to form cinchoninic acid, by reaction with benzoyl chloride to form the dibenzoate (IV), and by lead tetraacetate oxidation to produce cinchoninaldehyde, which was isolated as its phenylhydrazone or p-nitrophenylhydrazone (V).[2]



$$3\ \underset{\text{(I)}}{\text{Q-4-CHO}} \xrightarrow{\text{aq. alc. KCN}} 1\ \underset{\text{(II) 85–90\%}}{\text{Q-4-CHOH—CHOH-4-Q}} + 1\ \underset{\text{(III) 95–100\%}}{\text{Q-4-COOH}}$$

$$\text{(I)} \xrightarrow{\text{KCN}} \underset{\text{possible intermediate}}{\underset{\text{(IIa)}}{\text{(Q-4-COCHOH-4-Q)}}} \xrightarrow{\text{Q-4-CHO + KCN}} \text{(II)}$$

The results can be explained by considering the benzoin (IIa) to be formed as an intermediate which then undergoes an intermolecular oxidation–reduction (modified Cannizzaro) with more of the aldehyde to give the final products II and III.

Formation of the hydrobenzoin directly in the benzoin condensation (and other evidence) led the author to suspect that cinchoninaldehyde might undergo the Cannizzaro reaction more readily than many aromatic aldehydes. The reaction

$$\underset{\text{(I)}}{\text{2Q-4-CHO}} \xrightarrow{\text{aq. KOH}} \underset{\text{(III)}}{\text{Q-4-COOH}} + \underset{\text{(VI)}}{\text{Q-4-CH}_2\text{OH}}$$

was effectively quantitative over a range of alkali concentrations, though with a very dilute solution the neutral (alcohol) fraction was found to contain nearly equal amounts of VI and the hydrobenzoin II. The quinolyl-4-methanol was further characterized by preparation of the phenyl and α-naphthyl urethans.

In an attempt to correlate this facile Cannizzaro reaction with the results in the benzoin reactions, an experiment was tried using a base of the same order of base-strength as potassium cyanide but one which does not produce the benzoin condensations. Such a base should be sodium metaborate ($NaBO_2$) since the acidic dissociation constants of hydrocyanic and boric acids are very nearly the same. Using this base, no isolable amounts of the quinoline acid or alcohol products were obtained and most of the aldehyde was recovered. This would suggest that bases of the strength of potassium cyanide or sodium metaborate do not readily produce the Cannizzaro reaction with cinchoninaldehyde itself, but does not necessarily preclude the possibility that such bases could cause a mixed intermolecular oxidation–reduction as suggested for the benzoin reaction.

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Experimental[3]

A. Benzoin Condensation with Cinchoninaldehyde.—Cinchoninaldehyde monohydrate, 1.5 g., was dissolved in 25–30 cc. of hot absolute methanol and 3 cc. of aqueous potassium cyanide solution (containing 0.9 g. of potassium cyanide) was added. The solution turned a deep blood red color at once and was heated on the steam-bath for one hour. A solid had started to precipitate within two or three minutes, and after heating for one hour the mixture was cooled, the precipitate filtered and washed with water and alcohol. After crystallization from aqueous pyridine, the yield of II was 0.8 g. (90% according to the disproportionation equation shown above), m. p. 204–205° (dec. to red oil).

Anal. Calcd. for $C_{20}H_{16}O_2N_2$: C, 75.92; H, 5.10; N, 8.86. Found: C, 75.91, 75.78; H, 5.17, 5.13; N, 8.50.

To the filtrate from the above precipitate was added 10 cc. of water and all alcohol was removed from the solution by evaporation on the steam-bath. The hot aqueous solution was filtered and then made neutral to congo red paper with concentrated hydrochloric acid. Cooling gave a white crystalline precipitate of cinchoninic acid (III); yield 0.5 g. (100% according to the disproportionation equation), m. p. 254–255°. A mixture with authentic cinchoninic acid showed no depression of the melting point.

Chromic Anhydride Oxidation of II.—A solution of 1.0 g. of II in 10 cc. of acetic acid was treated with 1 g. of chromic anhydride and heated two hours on the steam-bath. The resulting dark solution was filtered and evaporated to dryness *in vacuo*. After dilution of the residue with water, excess ammonium hydroxide was added and the precipitate was removed by filtration. The aqueous filtrate was evaporated to a small volume *in vacuo* and made neutral to congo red paper with dilute hydrochloric acid. Cooling gave 0.85 g. (80%) of white crystals, m. p. 254–255°. There was no melting point depression when a sample of the product was mixed with authentic cinchoninic acid.

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(1) Phillips, THIS JOURNAL, **67**, 744 (1945).

(2) Kwartler and Lindwall, *ibid.*, **59**, 524 (1937).

(3) All melting points are uncorrected.

Benzoylation of II.—To a solution of 1.0 g. of II in 50 cc. of hot anhydrous pyridine was added 2 cc. of benzoyl chloride with thorough mixing, and the whole was heated for two hours on the steam-bath. The solution gradually turned a deep red color, and after two hours it was evaporated to dryness *in vacuo*. The residue was heated for one hour on the steam-bath with water, and, after cooling, the water was decanted from the precipitated pasty solid. On recrystallization from much absolute alcohol there was obtained 0.94 g. (60%) of white crystals of the dibenzoyl derivative; m. p. 275–276° (dec.).

Anal. Calcd. for $C_{34}H_{24}O_4N_2$: C, 77.83; H, 4.62. Found: C, 77.70; H, 4.71.

Lead Tetraacetate Oxidation of II.—Lead tetraacetate, 2 g., was dissolved in 10 cc. of warm acetic acid, 1.0 g. of II was added bit by bit, and the clear, pale-yellow solution was heated for one hour on the steam-bath. After cooling, 20 cc. of water was added, but no precipitate or color change resulted.

To this mixture was added a solution of 1.5 g. of *p*-nitrophenylhydrazine in 30 cc. of hot glacial acetic acid, followed by additional heating on the steam-bath for one hour. From the cooled solution 1.5 g. (85%) of yellow-brown solid precipitated, and, on crystallization from ethyl acetate, this gave yellow crystals, m. p. 263–264° (dec.).

Anal. Calcd. for $C_{16}H_{12}O_2N_4$: C, 65.73; H, 4.14. Found: C, 65.76; H, 4.16.

Cinchoninaldehyde Phenylhydrazone.[4]—Cinchoninaldehyde monohydrate, 1.7 g., yielded 2.5 g. (100%) of yellow crystals, crystallized from a benzene–hexane mixture, m. p. 175–176°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.70; H, 5.30. Found: C, 77.44; H, 5.24.

B. Cannizzaro Reaction with Cinchoninaldehyde.—The general procedure used was to mix the aldehyde (0.01 mole) with an amount of aqueous alkali (of various concentrations) which would contain at least 0.01 molecular equivalents of alkali. After heating from one to three hours on the steam-bath the mixture was cooled and filtered to remove the insoluble by-product. This was purified by crystallization from aqueous pyridine and was shown to be identical with the hydrobenzoin II, obtained in the benzoin reaction, by analysis and by determinations of melting point and mixed melting point with the product obtained in the other reaction.

The aqueous alkaline filtrate from II was thoroughly extracted with ether to remove all quinolyl-4-methanol (VI) formed (see below).

Finally the aqueous solution left from the ether extraction was made neutral to congo red paper with hydrochloric acid and was chilled to precipitate III. Cinchoninic acid was identified by melting point and a mixed melting point determination with an authentic specimen.

TABLE I

CANNIZZARO REACTION WITH TEN MILLIMOLES OF CINCHONINALDEHYDE

Alk. medium and concn.	Heating time at 100°C., hr.	Yield in millimoles[a] Cinchoninic acid (III)	4-Quinolylmethanol (VI)	Hydrobenzoin (II)
10 cc. 20% KOH	1	5	4.8	0.05 (trace)
10 cc. 5% KOH	1	5	4.5	0.03 (trace)
80 cc. 1% KOH	3	5	2.0	2.8
10 cc. 14% $NaBO_2$	1	0[b]	0	0

[a] Calculated as the number of millimoles of aldehyde stoichiometrically equivalent to the amount of the product which was isolated in each case. [b] The ether extract gave an 80% recovery of the aldehyde isolated as its condensation product with 2-thiohydantoin.[1]

4-Quinolylmethanol (VI).—This substance was obtained by evaporation of the ether extracts from the Cannizzaro reaction (see B above) and crystallized from benzene as white crystals, m. p. 99–100°.

Anal. Calcd. for $C_{10}H_9ON$: C, 75.42; H, 5.72; mol. wt., 159.1. Found: C, 75.61; H, 5.63; mol. wt., 169 (cryoscopic in camphor).

4-Quinolylmethanol Phenylurethan.[5]—This was obtained in quantitative yield as white crystals from benzene; m. p. 162–163°.

Anal. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.35; H, 5.07. Found: C, 73.53; H, 5.11.

4-Quinolylmethanol α-Naphthylurethan.[5]—This was obtained in quantitative yield as white crystals from benzene–hexane and was recrystallized from methanol; m. p. 157–158.5°.

Anal. Calcd. for $C_{21}H_{16}O_2N_2$: C, 76.81; H, 4.92. Found: C, 76.76; H, 5.18.

Summary

The behavior of cinchoninaldehyde in the benzoin and Cannizzaro reactions has been examined. In the benzoin reaction an unusual result was found, the hydrobenzoin analog and cinchonic acid being formed in equimolecular amounts. The Cannizzaro reaction proceeded rapidly and normally, except that the hydrobenzoin type of compound obtained from the benzoin was a by-product.

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[4] For general method of preparation of aryl hydrazones, see Oliver Kamm, "Qualitative Organic Analysis," 2nd edition, John Wiley and Sons, Inc., N. Y., p. 170.

[5] For method of preparation of urethans see ref. 4, p. 167.