[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SIR JOHN CASS COLLEGE]

The Reaction of Reissert Compounds and Related 1-Acyl-1,2-dihydroquinoline Derivatives[1]

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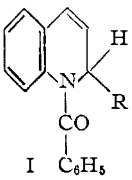
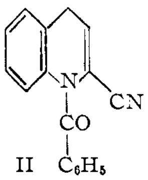
The ultraviolet absorption spectra of the Reissert nitrile and its dihydro derivative have been re-examined and shown to support the original formulation for the former compound. The Reissert acid has been prepared from the corresponding amide by a new method of selective hydrolysis on an acid ion-exchange resin. It has been shown that both the amide and the acid yield benzaldehyde after a preliminary dehydration and these results are discussed in relation to the Reissert reaction.

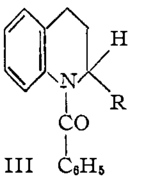
In 1905, Reissert[2] prepared a crystalline compound by the interaction of quinoline and benzoyl chloride in the presence of aqueous potassium cyanide, and to this he gave the formula 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = CN) to account in part for the production from it, by acid hydrolysis, of benzaldehyde and quinaldinic acid.



I



II



III

An investigation was undertaken to obtain further support for this formulation, to determine those structural features of the molecule which are necessary for this unusual mode of hydrolysis of a substituted amide and to provide a reasonable mechanism for that hydrolytic reaction.

The hydrogenation[3] of I under low pressure conditions gave some 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (III, R = CN)—also synthesized by an independent route—in support of structure I. A possible alternative formulation as 1-benzoyl-1,4-dihydroquinaldonitrile (II, R = CN) had been considered by Boekelheide and Weinstock,[4] but the similarities in the ultraviolet absorption spectra of I (R = CN), and of the 4- and 2,4-dimethyl derivatives prepared from I (R = CN) by direct methylation, led them to reject II, since only the 3,4-position is possible for the double bond in the 2,4-dimethyl derivative of I(R = CN).

However, McEwen, *et al.*,[5] maintained that the ultraviolet absorption spectra of I (R = CN) and of III (R = CN) were sufficiently similar to weaken this argument; but it was later concluded[3] that the sample of II (R = CN) used by McEwen was impure, and must have contained enough unchanged Reissert compound not only to give appreciable amounts of benzaldehyde on hydrolysis, but also to invalidate the conclusions drawn from a spectrum analysis on it. The spectra obtained from pure samples of I (R = CN) and III (R = CN) are reproduced in Fig. 1; they are clearly different, thus supporting Boekelheide and Weinstock's argument for structure I (R = CN) as the Reissert complex.

In attempts to determine those structural features of I (R = CN) which are necessary for the unusual mode of hydrolysis, some formally analogous compounds such as α-benzanilido-phenylacetonitrile and 2-benzanilido-4-phenylbut-3-enenitrile were prepared,[6] but both underwent normal hydrolysis to benzoic acid, as also did N-benzoyl-N-phenyl-glycinonitrile.[7] These observations suggest that the intact quinoline ring system is a requisite of this reaction, and the normal hydrolysis of III (R = CN) indicates the necessity of the 3,4-double bond in I (R = CN) for the abnormal hydrolysis to occur.

The normal hydrolysis to benzoic acid of 1-benzoyl-1,2-dihydroquinoline,[8] of 1-benzoyl-1,2-dihydroquinaldamide[9] and of 1-benzoyl-3-acetyl-1,2-dihydroquinaldinic acid[10] indicated that the 2-cyano group in I was also necessary for the occurrence of abnormal hydrolysis. However, it has now been shown that the latter two compounds can also give benzaldehyde on hydrolysis, provided that they are first treated with either polyphosphoric acid or thionyl chloride. It could be argued that a regeneration of the 2-cyano group would account for the results on the amide; those on the acid require a different explanation.

Further, although it would be expected that the 3-acetyl group is without significance in these reactions, it obviously was better to subject the unsubstituted Reissert acid (I, R = CO_2H) to the same treatment.

Attempts to convert 1-benzoyl-1,2-dihydroquinaldamide to the Reissert acid by the standard methods were unsuccessful; but this has now been achieved[11] by a selective hydrolysis of the 2-carbamoyl group on an acidic ion-exchange resin (Amberlite IR 120). It was considered that the more strongly polar character and association effects of an unsubstituted amide group[12] might lead to a preferential hydrolysis of the 2-carbamoyl group at the surface of a suitable ion-exchange resin. This was realized in a yield of 61%, by gently refluxing a solution of the amide I (R = $CONH_2$) in acetone containing a 1.5-mole proportion of

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[1] Taken in part from a thesis submitted by R. F. Collins in partial fulfillment of the requirements for the Ph.D. degree, University of London, England.

[2] A. Reissert, *Ber.*, **38**, 1603 (1905).

[3] R. F. Collins, THIS JOURNAL, **77**, 4921 (1955).

[4] V. Boekelheide and J. Weinstock, *ibid.*, **74**, 660 (1952).

[5] W. E. McEwen, R. H. Terss and I. W. Elliott, *ibid.*, **74**, 3605 (1952); see also ref. 14.

[6] R. F. Collins and T. Henshall, *J. Chem. Soc.*, 1881 (1956).

[7] I. W. Elliott, THIS JOURNAL, **77**, 4408 (1955).

[8] R. F. Collins, *J. Chem. Soc.*, 3641 (1954).

[9] W. E. McEwen and R. L. Cobb, THIS JOURNAL, **77**, 5042 (1955).

[10] R. B. Woodward and E. C. Kornfeld, *ibid.*, **70**, 2508 (1948).

[11] R. F. Collins, *Chemistry & Industry*, 736 (1957).

[12] T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, 1942, p. 143.

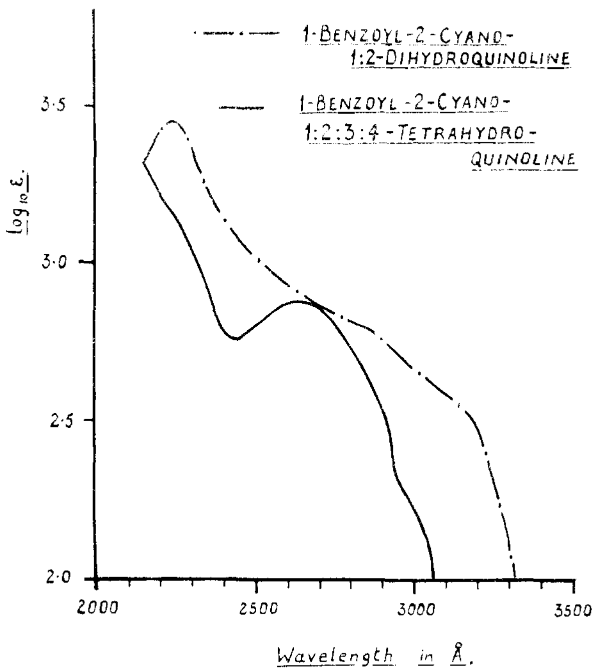


Fig. 1.

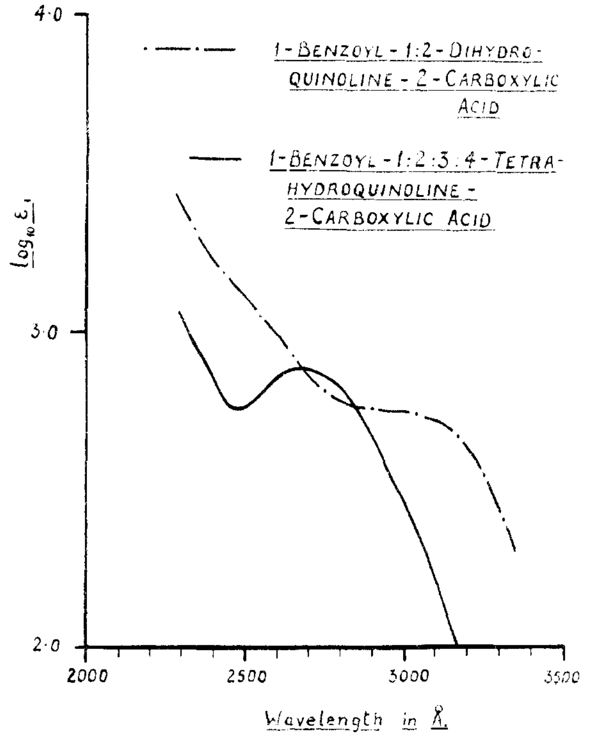
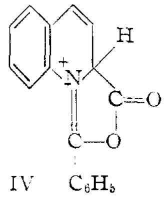


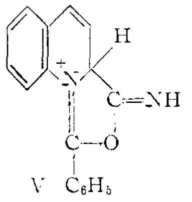
Fig. 2.

water with the powdered resin. The structure of the product was confirmed by hydrogenation to III (R = CO_2H). Further work on this reaction is being pursued actively in this and related fields of study.

It is interesting to note that in the ultraviolet absorption spectra (Fig. 2) of the Reissert acid I (R = CO_2H) and its hydrogenation product III (R = CO_2H) there is again a general shift to longer wave lengths in the former. Treatment of the Reissert acid with polyphosphoric acid, followed by hydrolysis in cold water, gave 74% of benzaldehyde isolated as its 2,4-dinitrophenylhydrazone; the hydrogenated acid III (R = CO_2H) was unchanged after the same treatment. The identical behavior of the Reissert acid and of the 3-acetyl derivative, in that both give benzoic acid on acid hydrolysis and benzaldehyde after a preliminary dehydration, serves to confirm the structure originally proposed for the 3-acetyl-1,2-dihydroquinaldinic acid intermediate by Woodward and Kornfeld.[10]

The preliminary treatment of the Reissert acid I (R = CO_2H) with polyphosphoric acid, thionyl chloride, sulfuric acid or with acetic anhydride is most likely to involve a dehydration since these reagents generally remove the elements of water from suitable structures. It was noted, however, that the best yield of benzaldehyde occurred in a strongly acidic dehydrating medium (polyphosphoric acid) and, by analogy with recent work on the formation of an oxazolonium ion from N-benzoylsarcosine in concentrated sulfuric acid,[13] it seems probable that IV would be formed initially from I (R = CO_2H) under these conditions. A cryoscopic investigation of the Reissert acid I (R = CO_2H) in concentrated sulfuric acid is now being pursued. If the equilibrium favors the formation of IV then no less than four ions should be detected in the solution. Since an analogous structure V has been postulated[14] to account for the formation of benzaldehyde from the Reissert nitrile I (R = CN) in aqueous acid, it can be seen that considerable interest attaches to a study of the Reissert acid I (R = CO_2H), under conditions which ultimately yield benzaldehyde.


IV


V

Experimental[15]

1-Benzoyl-1,2-dihydroquinaldamide.—1-Benzoyl-1,2-dihydroquinaldonitrile (15 g.) was hydrolyzed as described by McEwen and Cobb[9]; but after the addition of water (600 ml.) to the concentrate containing the crude amide, it was found preferable to store the mixture at 0–5° for 24 hr. During this period of standing the crude product became fully crystalline, and was easy to collect. One recrystallization from aqueous ethanol gave the pure amide (8.6 g., m.p. 168–170°).

Reaction of 1-Benzoyl-1,2-dihydroquinaldamide with Polyphosphoric Acid.—1-Benzoyl-1,2-dihydroquinaldamide (0.200 g.) was heated with polyphosphoric acid (6.0 g.) at 100° for 25 min. to complete solution. The deep-red solution was poured on to ice, slowly decomposed and treated with a solution of 2,4-dinitrophenylhydrazine (0.22 g.) in 4 *N* sulfuric acid to isolate the benzaldehyde produced. The yield of crude derivative (0.123 g., m.p. 233–235°) corresponded to about 57% of benzaldehyde under these conditions. Recrystallization raised the m.p. of the derivative to 238–239° with a recovery of 82%.

Straightforward acid hydrolysis of the amide,[9] without prior treatment with polyphosphoric acid, gave only benzoic

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(13) J. L. O'Brien and C. Niemann, This Journal, **79**, 80 (1957).

(14) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, 511 (1955).

(15) All m.p.'s are uncorrected.

acid. 1-Benzoyl-1,2,3,4-tetraquinaldamide failed to give benzaldehyde after treatment with polyphosphoric acid.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile with Polyphosphoric Acid.—1-Benzoyl-1,2-dihydroquinaldonitrile (0.200 g.) was heated with polyphosphoric acid (6 g.) at 100° for 20 min. The deep-orange solution was decomposed with ice-water, and the benzaldehyde isolated as the 2,4-dinitrophenylhydrazone (0.2062 g., m.p. 236–238°). The yield of derivative corresponded to 94% of benzaldehyde from I under these conditions, and this method of hydrolysis may prove to be the most convenient general procedure for converting Riessert compounds into the corresponding aldehydes.

When 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile was subjected to the same conditions, only a pale-yellow solution resulted which did not give benzaldehyde on hydrolysis.

1-Benzoyl-1,2-dihydroquinaldinic Acid.—1-Benzoyl-1,2-dihydroquinaldamide (4.2 g.) was dissolved in acetone (100 ml.) containing a small quantity of water (0.45 ml.). Powdered acid ion-exchange resin (14.5 g. of Amberlite IR 120, 4.1 meq. passing a 60-mesh sieve) was added, and the mixture refluxed under vigorous stirring for 22 hr. The resin was collected, the filtrate concentrated *in vacuo* to about 30 ml. and water (150 ml.) added. Potassium carbonate (6 g.) was dissolved in the mixture, and undissolved material removed in ether (100 ml.). The aqueous alkaline solution was cooled and after acidification with 2 *N* hydrochloric acid, the product crystallized slowly and was collected (2.55 g., m.p. 163–164° dec. with effervescence). *Anal.* Calcd. for $C_{17}H_{13}O_3N$: C, 73.1; H, 4.7; N, 5.0. Found: C, 72.9; H, 4.8; N, 5.2.

Titration of the recovered resin showed that a 78% release of ammonia from the amide had occurred, but the yield of acid isolated was only 61%, and 0.3 g. of unchanged amide was recovered, albeit with difficulty, from the ethereal extract of non-acidic material.

1-Benzoyl-1,2,3,4-tetrahydroquinaldinic Acid.—1-Benzoyl-1,2-dihydroquinaldinic acid (0.3 g.) in ethanol (15 ml.) was hydrogenated over platinum oxide (0.05 g.) under a pressure of hydrogen slightly greater than one atmosphere and at room temperature; the absorption corresponded exactly to one molar proportion. The catalyst was collected and a little water added to the filtrate to promote crystallization. The product (0.17 g., m.p. 186–188°) was collected and identified by mixed melting point with an authentic sample of 1-benzoyl-1,2,3,4-tetrahydroquinaldinic acid.[3] The mother liquors provided a further crop (0.1 g., m.p. 184–186°) on dilution with water.

The Hydrolysis of 1-Benzoyl-1,2-dihydroquinaldinic Acid by Aqueous Acid.—1-Benzoyl-1,2-dihydroquinaldinic acid (0.5 g.) was refluxed for 3 hr. with a mixture of water (5 ml.) and concentrated hydrochloric acid (5 ml.) containing a trace of wetting agent (Lissapol). Complete solution occurred only after 2.5 hr.; a similar resistance to hydrolysis also was shown by the 3-acetyl derivative.[10] No benzaldehyde could be detected in the hydrolysate but after cooling, benzoic acid (0.17 g., m.p. 121–122°) separated.

The filtrate was neutralized with 2 *N* sodium hydroxide and then just acidified to litmus with 2 *N* acetic acid. A gummy product separated but could not be purified; and an attempt to isolate the 1,2-dihydroquinaldinic acid as a copper salt also failed to give a pure product.

Reaction of 1-Benzoyl-1,2-dihydroquinaldinic Acid with Polyphosphoric Acid.—1-Benzoyl-1,2-dihydroquinaldinic acid (0.200 g.) was heated at 100° with polyphosphoric acid (6 g.) for 0.25 hr. The deep-yellow solution in which bubbles appeared, was decomposed with ice-water, and benzaldehyde again isolated as its 2,4-dinitrophenylhydrazone (0.152 g., m.p. 238–239°) in amount corresponding to 74% of benzaldehyde.

A similar experiment involving 1-benzoyl-1,2,3,4-tetrahydroquinaldinic acid (0.200 g.) and polyphosphoric acid gave only a pale yellow solution from which the acid (0.13 g., m.p. 186–188°) was recovered unchanged, and no benzaldehyde could be detected.

Effects of Other Dehydrating Agents on 1-Benzoyl-1,2-dihydroquinaldinic Acid. (1) **Thionyl Chloride.**—The acid (0.5 g.) was dissolved in thionyl chloride (2 ml.) at 0°. After 10 min. at room temperature, the orange-colored solution was decomposed with ice, made just alkaline with 2 *N* sodium hydroxide and steam distilled. Benzaldehyde 2,4-dinitrophenylhydrazone (0.137 g., m.p. 233–235°) was isolated from the distillate; the yield of crude product corresponding to about 26% of benzaldehyde. Recrystallization from acetic acid gave the pure derivative (0.120 g., m.p. 238–239°). The original mother liquors were acidified with 2 *N* hydrochloric acid and some benzoic acid separated (0.1 g., m.p. 120–121°). A crude copper salt (0.2 g.) was isolated from the acid mother liquors after first making alkaline with 2 *N* NaOH, and then just acid with acetic acid; but attempts to isolate a pure acid from it were unsuccessful.

(2) **Acetic Anhydride.**—A qualitative test with acetic anhydride gave an orange-colored solution, from which a trace of benzaldehyde was isolated after decomposition with water. It is noteworthy that if the solution in acetic anhydride is refluxed for several minutes, no benzaldehyde can be detected on addition of water to the reddish-brown solution.

(3) **Concentrated Sulfuric Acid.**—1-Benzoyl-1,2-dihydroquinaldinic acid dissolves in concentrated sulfuric acid to a deep-yellow solution which gives some benzaldehyde after pouring on to crushed ice. A precisely similar result was obtained with the Reissert nitrile I (R = CN) and sulfuric acid.

1-Benzoyl-3-acetyl-1,2-dihydroquinaldinic Acid.[10]—Ethyl 1-benzoyl-2-acetyl-1,2-dihydroquinaldate[10] (1.4 g.) was dissolved in methanol (20 ml.) and treated with a solution of potassium bicarbonate (0.5 g.) in water (3 ml.). The solution was refluxed for 4 hr., concentrated *in vacuo* and some water was added to the residue. The red solution was filtered to remove some undissolved material, acidified, and the crude product collected. Recrystallization from aqueous ethanol yielded the pure 1-benzoyl-3-acetyl-1,2-dihydroquinaldinic acid (1 g., m.p. 197–198° dec. and effervescence) (Woodward and Kornfeld[10] give m.p. 198–199° dec.). *Anal.* Calcd. for $C_{19}H_{15}O_4N$: C, 71.0; H, 4.7; N, 4.37. Found: C, 71.1; H, 4.8; N, 4.45.

Reaction of 1-Benzoyl-3-acetyl-1,2-dihydroquinaldinic Acid with Thionyl Chloride.—The acid (0.4 g.) was suspended in dry benzene (10 ml.) and treated with thionyl chloride (2 ml.). A red oil slowly separated and the mixture was stored for 24 hr. (it is now realized that the reaction is probably complete in much less time). The solvent was removed *in vacuo* and the residue decomposed with ice. Benzaldehyde was steam distilled from the mixture and identified as the 2,4-dinitrophenylhydrazone (0.02 g., m.p. 236–237°, after recrystallization from acetic acid).

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