[Contribution from Radio-Carbon Laboratories]

Studies with Quinolines. II. The Acid-Catalyzed Hydrolysis of Reissert Compounds

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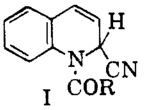
The cyclic imine X has been prepared from 2-benzoyl-1,2-dihydroisoquinaldonitrile, II, on treatment of the latter with hydrobromic acid in acetic acid. The imine was isolated and purified and was found to be stable on treatment with water. The formation of cyclic imines of this type appears to be a general characteristic of Reissert compounds. On decomposition in hydrobromic acid–acetic acid the imine X gives benzaldehyde, isoquinaldamide hydrobromide and the hydrobromide of isoquinaldic acid. On treatment of the hydrobromide of quinaldic acid with thionyl chloride there is loss of hydrogen bromide with formation of the free acid chloride. This route eliminates the necessity of isolating the anhydrous acid.

Reissert compounds or 1-acyl-1,2-dihydroquinaldonitriles, I, 2-acyl-1,2-dihydroisoquinaldonitriles, II, and analogous compounds, when treated with mineral acid, undergo hydrolysis to aldehydes, acid amides, and carboxylic acids. The formation of aldehydes by hydrolysis of these compounds involves a mechanism more complex than the simple hydrolysis of a nitrile to an amide and carboxylic acid. Several mechanisms have been proposed for this unusual behavior of Reissert compounds, but there has been insufficient experimental evidence in support of the several mechanisms predicted by theoretical considerations.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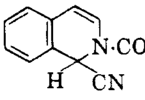
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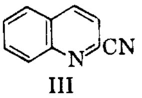
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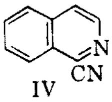
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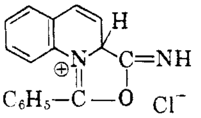
In early studies[1-3] of the mechanism of the acid-catalyzed hydrolysis of Reissert compounds, it was assumed that the nitriles, III and IV, were formed as intermediates which were subsequently hydrolyzed to the amides and carboxylic acids. This assumption was never proved, however, and Cobb and McEwen[4] offered experimental evidence which indicates that the nitrile is not one of the products of the hydrolysis. These authors found that on treatment of I (R = benzoyl) with ethanolic hydrogen chloride no quinaldonitrile could be isolated from the reaction mixture. Similar studies in concentrated hydrochloric acid afforded only benzaldehyde, quinaldamide, quinaldic acid, benzoin quinaldate, and unchanged I. On the other hand, when mole quantities of I and quinaldonitrile were treated in the same manner, 11 to 39% of the nitrile was recovered unchanged. They then proposed a mechanism which excluded the nitrile as an intermediate and which could, on a theoretical basis, explain the formation of all the products isolated from a typical reaction. It was assumed that the Reissert compound I on treatment with hydrochloric acid first gives the cyclic intermediate V which rearranges to VII through the mesoionic intermediate VI. Addition of water to VII gives VIII which then collapses to benzaldehyde and the amide IX.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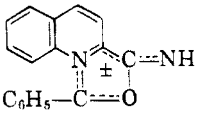
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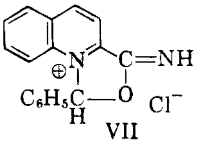
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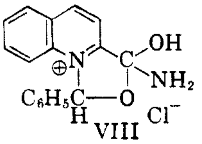
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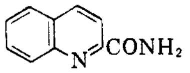
IX

None of the previous workers were able to isolate in pure form any of the proposed cyclic intermediates.[5] It was this lack of experimental evidence that prompted us to reinvestigate the hydrolysis of Reissert compounds.

In a previous communication[6] we were able to show that a Reissert compound I (R = benzoyl) on treatment with hydrobromic acid in acetic acid gives good yields of benzaldehyde and quinaldic acid. We have repeated this reaction with 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), with similar results and were able to isolate in 95% yield the hydrobromide analog of one of the cyclic intermediates proposed by Cobb and McEwen.[4] This intermediate or Reissert imine

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(1) W. E. McEwen and R. N. Hazlett, *J. Am. Chem. Soc.*, **71**, 1949 (1949).

(2) M. Colonna, *Gazz. chim. ital.*, **82**, 503 (1952).

(3) C. G. Swain and W. A. Sheppard, Abstracts of papers presented at ACS National Meeting, Cincinnati, Ohio, March 29 to April 7, 1955, P40N.

(4) R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(5) McEwen and co-workers did, however, obtain unstable yellow precipitates which could not be purified and which decomposed with water to give benzaldehyde and quinaldamide. Haworth and Perkin obtained an orange compound when a chloroform solution of 2-benzoyl-6,7-dimethoxy-1,2-dihydroquinaldonitrile was treated with hydrogen chloride. This orange substance gave benzaldehyde and 6,7-dimethoxyisoquinaldamide upon steam distillation [R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 1434 (1925)].

(6) J. W. Davis Jr., *J. Org. Chem.*, **24**, 1691 (1959).

X[7] may be crystallized from hot alcohol and does not decompose on treatment with hot or cold water. It can be isolated with ease in a high state of purity. Upon decomposition it gives benzaldehyde, isoquinaldamide hydrobromide XI, and isoquinaldic acid hydrobromide XII.

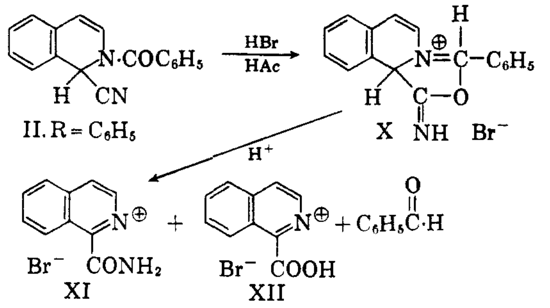
When 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), is added to a mixture of hydrobromic acid in acetic acid there is an intermediate color change from colorless to bright yellow which gradually changes to deep orange over a period of about 5 minutes. By this time the suspended Reissert compound has completely dissolved. Some minutes later the imine X begins to separate and is complete within 2 to 3 minutes. If the imine is allowed to remain in contact with the acid medium, an exothermic reaction takes place, converting it to the amide hydrobromide, the acid hydrobromide, and benzaldehyde.

The catalytic formation of this cyclic imine X appears to be instantaneous. If the temperature is maintained at 20°, the rate of reaction seems to depend on the solubility of the Reissert compound in the reaction medium; its subsequent precipitation may be compared to crystallization from a supersaturated solution. The breakdown of the imine X to benzaldehyde and the acid amide hydrobromide evolves heat and is favored by the catalytic medium of hydrobromic acid in acetic acid. No Reissert compound could be isolated from the mother liquors and the odor of benzaldehyde was absent. When the mother liquors were placed in the deep freeze at −10° for 24 hours some isoquinaldamide hydrobromide crystallized. We may assume that this amide hydrobromide was derived from a small amount of the imine which remained in solution since isoquinaldamide hydrobromide is much less soluble in the reaction medium than the cyclic imine X and would have been removed in the original filtration. The odor of benzaldehyde was apparent.[8]

When hydrochloric acid in acetic acid was used as the hydrolysis medium, the color changes and the time for complete solution were the same as in the case of hydrobromic acid in acetic acid. There was no odor of benzaldehyde or immediate precipitation of the imine hydrochloride. Addition of excess water did hot precipitate any unchanged Reissert compound. When the reaction mixture was allowed to stand overnight at room temperature, crystals were formed and there was still no evidence of the presence of benzaldehyde.[9]

The formation of Reissert imines from Reissert compounds appears to be a general reaction and under the proper conditions, particularly when acetic acid is used as solvent, only one equivalent of mineral acid is necessary. The experimental evidence presented below indicates that the acid-catalyzed hydrolysis of Reissert compounds proceeds as follows: Reissert compound → Reissert imine → acid amide + aldehyde + acid.

Or in the example studied here



When the hydrobromides of quinaldic and isoquinaldic acid are treated with thionyl chloride there is loss of hydrogen bromide with formation of the free acid chlorides. This route to the acid chlorides is preferred since a purer product is obtained and the necessity of passing through the anhydrous acids is eliminated.

The quinaldyl radical reacts readily with primary and secondary amino groups to give highly crystalline derivatives.[6,10] The isoquinaldyl radical may be used in like manner.

EXPERIMENTAL[11]

2-Benzoyl-1,2-dihydroisoquinaldonitrile, II. This compound was prepared according to the procedure of Reissert as modified by Padbury and Lindwall.[12] The yield from isoquinoline[13] was approximately 50% after two crystallizations from absolute ethanol. The product melted at 125–126°.

Reissert imine X. *Action of hydrobromic acid–acetic acid on* II. Ten g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), as prepared above were suspended in 100 ml. of glacial acetic acid and the mixture stirred vigorously while cooled in a water bath at 20°. Ten ml. of 47% hydrobromic acid were added. After about 5 min. all of the solid had dissolved and the solution was dark orange. The stirring

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(7) Since this appears to be a general reaction leading to a new series of compounds, for convenience we will call them "Reissert imines."

(8) The imine will decompose quantitatively when treated with the sulfuric acid solution of 2,4-dinitrophenylhydrazine, giving benzaldehyde 2,4-dinitrophenylhydrazone, the acid amide and acid.

(9) The isolation of the several mineral acid salts of Reissert compounds derived from quinoline, isoquinoline, ring-substituted quinolines, and ring-substituted isoquinolines will be presented in a future communication.

(10) The application of the several ring-substituted acid chlorides, particularly the 2- and 5-nitro derivatives, to the identification of primary and secondary amino compounds will be presented at a later date. It is interesting to note that some of the amide derivatives of quinoline inhibit the growth of Ehrlich Ascites tumor in mice with prolongation of life. Of particular interest was quinaldylalanine which showed a T/C of 0.09 (unpublished data).

(11) All melting points are uncorrected. The analyses were performed by Dr. Elek of Los Angeles, Calif., and Drs. Weiler and Strauss of Oxford, England.

(12) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

(13) The isoquinoline was obtained from Eastman Kodak and melted at 26–27°.

was continued and after about 3 min. the imine X began to separate. Stirring was continued for several minutes more after which the bright yellow crystals were collected on a glass centered funnel and washed with glacial acetic acid until the washings were almost colorless. The crystals were washed with ether and dried in vacuum over sodium hydroxide. The product weighed 12.5 g. and melted at 158–160°. On recrystallization from hot methanol there was obtained 9.0 g. of pale yellow prismatic needles which melted at 159–160°. A recrystallized sample was dried in vacuum over phosphorus pentoxide at 80° for 24 hr.

Anal. Calcd. for $C_{17}H_{13}ON_2HBr$.C, 59.65; H, 4.09; Br, 23.39; N, 8.18. Found: C, 59.70; H, 4.01; Br, 23.31; N, 8.21.

Action of hydrobromic acid–acetic acid on the Reissert imine X. A 13.4-g. sample of the imine was suspended in 10 ml. of 48% hydrobromic acid in 10 ml. of glacial acetic acid. the flask was set up to reflux and heated on a steam bath for 10 min. On cooling, 50 ml. of acetone was added and the crystals were collected and washed with acetone. On air drying the product weighed 9.0 g. The filtrate and washings were combined (Solution A) and worked up as described below. The 9 g. of material was suspended in 75 ml. of hot methanol and water added until all had dissolved. On refrigeration overnight 3 g. of light yellow crystals was obtained which melted at approximately 260°. [The mother liquors were saved (Solution B).] On recrystallization from 75% acetic acid or ethanol–isopropyl ether approximately 2.5 g. of colorless needles was obtained which melted at 272–273°. The analytical sample melted at 275–276°.

Anal. Calcd. for $C_{10}H_9ON_2Br$. C, 47.43; H, 3.55; Br, 31.59; N, 11.07. Found: C, 47.56; H, 3.88; Br, 31.10; N, 11.38.

This compound was found to be identical with the hydrobromide of isoquinaldamide. It sublimes at 250° without decomposition and when treated with aqueous ammonia gives isoquinaldamide which melts at 167–168°.

The mother liquors (Solution B) were evaporated to dryness to give approximately 6 g. of a light yellow solid. This was recrystallized from 85% acetic acid to give almost colorless needles which melted at 199–200°. A recrystallized sample dried over phosphorus pentoxide at 80° for 24 hr. was analyzed.

Anal. Calcd. for $C_{10}H_8O_2BrN$. C, 47.10; H, 3.14; N, 5.51; Br, 31.40. Found: C, 47.32; H, 3.32; N, 5.47; Br, 30.81. This was found to be identical with the hydrobromide of isoquinaldic acid. It may be sublimed at about 100° and 1 mm. pressure.

The original acetone-acid mother liquors (Solution A) were steam distilled. From the distillate was isolated an 85% yield of redistilled benzaldehyde.[14]

Action of water on the Reissert imine X. One g. of the cyclic imine X was suspended in 25 ml. of water and the mixture stirred for 30 min. There was no evidence of decomposition or odor of benzaldehyde. The crystals were collected by filtration and dried in a desiccator under vacuum. About 90% of the material was recovered and had a melting point of 159–160° identical with that of the starting imine X. A mixture of the two gave the same melting point. The same reaction was repeated with refluxing for 30 min. with similar results.

Isoquinaldic acid from isoquinaldic acid hydrobromide. Due to the difference in solubility of quinaldic acid and isoquinaldic acid, the latter could not be isolated in comparable yields as previously described for quinaldic acid.[6] The following procedure was therefore used for the isolation:

Ten g. of isoquinaldic acid hydrobromide (crystallized from a 1:1 mixture of 48% hydrobromic acid and glacial acetic acid) was dissolved in 20 ml. of water and a slight excess of concentrated ammonium hydroxide added. The resulting solution was boiled to remove excess ammonia and after cooling adjusted to *p*H5 with hydrochloric acid. The mixture was evaporated under reduced pressure and the residue extracted with hot benzene. On concentration and cooling isoquinaldic acid crystallized. The yield of recrystallized acid melting at 159–160° was 5.8 g. or approximately 85%.

Quinaldyl chloride from quinaldic acid hydrobromide. Ten g. of quinaldic acid hydrobromide[15] were suspended in 100 ml. of thionyl chloride[16] contained in an apparatus set up to reflux and protected from moisture by means of a calcium chloride tube. The flask was warmed gently at first, the temperature being gradually increased so that hydrogen chloride passed smoothly through the top of the condenser. After the hydrobromide had dissolved, the solution was refluxed for an additional 0.5 hr. (total 3.5 hr.). The thionyl chloride was removed under reduced pressure and the pale yellow crystals were taken up in approximately 50 ml. of hot anhydrous ether. On cooling in the refrigerator overnight clusters of pale yellow needles were obtained which melted at 95–96°. A mixed melting point with an authentic sample was essentially the same. The conversion is quantitative but only when the acid hydrobromide is anhydrous. When the hydrated form is used approximately 25% of the material does not dissolve in ether. This is probably due to the formation of the acid chloride hydrochloride. The same result occurs when the free hydrated acid is used to prepare the acid chloride.

VAN NUYS, CALIF.

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(14) A dark oily material remained in the flask after completion of the steam distillation. This material has been described previously [see ref. 1. Also see A. Reissert, *Ber.*, **38**, 3415 (1905)].

(15) Dried in a vacuum oven at approximately 100° for 3 hr.

(16) Distilled from linseed oil.