4. Adaptability to desiccation at elevated temperatures.

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UNIVERSITY OF VIRGINIA,
January 2, 1917.

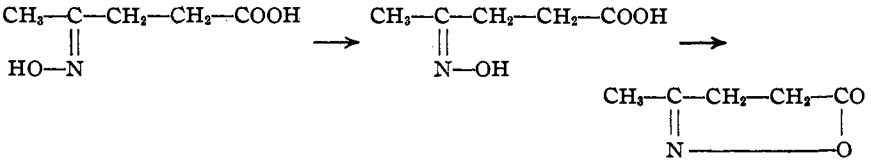
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WASHINGTON.]

ANHYDROXIMES. II.

BY ROBERT EVSTAFIEFF ROSE AND WINFIELD SCOTT, JR.[1]

Received November 8, 1916.

The β, γ and δ oximino acids, *i. e.*, the oximes of β, γ and δ carbonyl acids, show a strong tendency to lose water between the carboxyl and oximino groups, being thereby converted into ring structures containing carbon, oxygen, and nitrogen. For these cyclic compounds, whose properties are intermediate between those of lactones and acid anhydrides, one of us has suggested the name "anhydroxime."[2] The tendency towards ring formation in the oximino acids is greater than it is in the case of dicarboxylic acids but less than it is in the hydroxy acids. Thus acid anhydrides are usually formed only under the influence of heat or of a dehydrating agent and the rings formed are five or six membered;[3] lactones form spontaneously in the case of γ and δ hydroxy acids, while lactone rings of four to eight members have been prepared. Anhydroximes are formed spontaneously to give five and six membered cyclic compounds. Too little has been done to allow of stating that the ring cannot contain more or less atoms, but it would at least appear that ring formation does not proceed as readily as in the case of hydroxy acids. In this connection it should be remembered that configuration may influence the ease of formation of an anhydroxime, *e. g.*, the oxime of levulinic acid loses water only on prolonged heating with sulfuric acid,[4] but its behavior on undergoing the Beckmann rearrangement shows it to possess the *anti* configuration; inversion must then precede dehydration.



$$\begin{array}{l}\mathrm{CH_3-C-CH_2-CH_2-COOH}\\ \qquad\;\; \|\\ \mathrm{HO-N}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_3-C-CH_2-CH_2-COOH}\\ \qquad\;\; \|\\ \qquad\;\mathrm{N-OH}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_3-C-CH_2-CH_2-CO}\\ \qquad\;\; \| \qquad\qquad\qquad |\\ \qquad\;\mathrm{N}\text{—————}\mathrm{O}\end{array}$$

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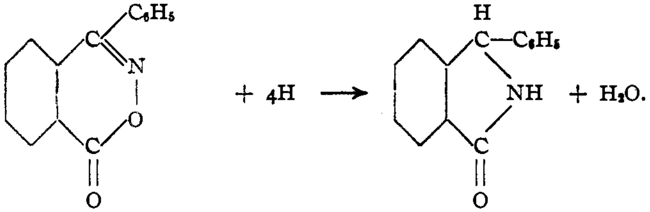
[1] The material presented here is used by Mr. Winfield Scott in his thesis in part fulfillment of the requirements for the M.S. degree of the University of Washington.

[2] Rose, THIS JOURNAL, 33, 388 (1911).

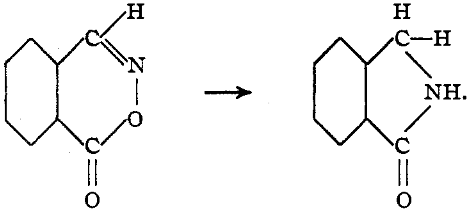
[3] The existence of malonic anhydride is due to a special reaction, that of carbon suboxide on acetic acid. The so-called anhydrides of the higher homologs of glutaric acid appear to possess much higher molecular complexity than they should were they really internal anhydrides.

[4] Rischbieth, *Ber.*, 20, 2669 (1887); Hantzsch and Werner, *Ibid.*, 23, 11 (1890).

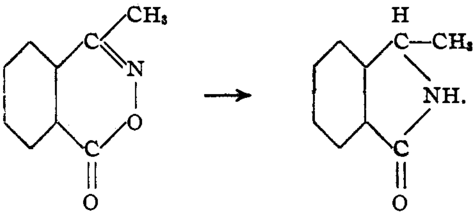
When *o*-benzoyl benzoic anhydroxime is reduced in acid solution, it yields 1-phenyl-phthalimidine.[1]



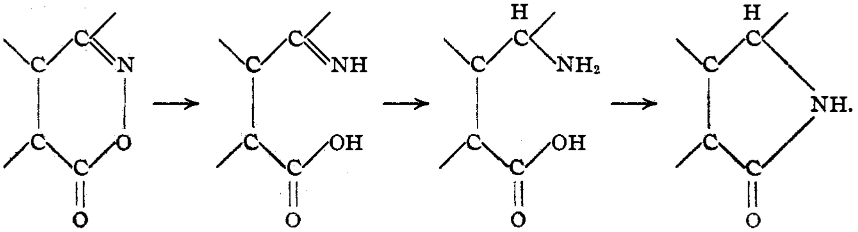
The present investigation was undertaken to ascertain whether hydrogenation followed a similar course in other γ-oximino anhydrides and, further, whether β-oximino anhydrides would behave in a like manner. It was found that *o*-aldehydo benzoic anhydroxime gave phthalimidine,



while *o*-acetyl benzoic anhydroxime was converted into 1-methyl-phthalimidine.



The reaction is, therefore, common to the three analogously constituted compounds. It represents a transition from a six to a five membered ring. The mechanism of the reduction is not clear; the most reasonable assumption appears to be that hydrogenation results in the opening of the anhydroxime ring with the formation of an imido acid, which is further reduced to an amino acid, this being followed by the elimination of water to give the lactam.



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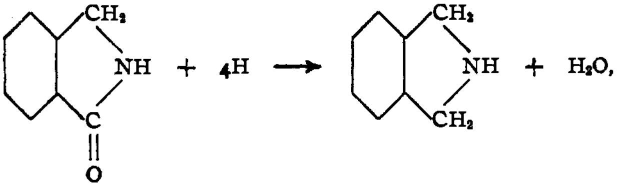
[1] Rose, *Loc. cit.*

In support of this view it may be stated that all efforts to produce elimination of the bridge oxygen alone are unsuccessful. Thus, in the reduction of *o*-acetyl benzoic anhydroxime, no 1-methyl-3-keto-isoindole is formed under conditions which should favor its production.

It is evident that reduction might well proceed further, the lactam carbonyl becoming involved. This is actually observed to be the case, *o*-aldehydo benzoic anhydroxime giving dihydroisoindole,



while *o*-acetyl benzoic anhydroxime gives 1-methyl-dihydroisoindole.

Whether the reaction can be still further modified to yield oximino aldehydes, *i. e.*, to behave as do the lactones of gluconic acid and its isomers, the authors are unable to state because of lack of material consequent upon the impossibility of obtaining further supplies of hydroxylamine hydrochloride. It is hoped to make this the subject of a future paper.

The anhydroximes of β-carbonyl acids behave very differently. It was thought that reduction might lead to the formation of tetratomic rings containing nitrogen, these being known to be capable of existence though unstable.[1]

In fact β-oximino butyric anhydroxime gives ammonia and butyric acid, though a sticky gum is also produced. In this case the reduction of the latent oximino group follows the usual course, giving aminobutyric acid which is in turn reduced to free ammonia and butyric acid.[2] The authors do not consider their results to be conclusive because of the inadequate quantity of material at their disposal.

The anhydroximes of aliphatic γ-carbonyl acids have yet to be examined.

Experimental Part.

Reduction of *o*-Acetyl Benzoic Anhydroxime.—*o*-Aldehydo benzoic acid was prepared according to the directions given by Graebe and Trümpy,[3] the necessary phthalonic acid being made by the oxidation of naphthalene using Tscherniac's method.[4]

The aldehydo benzoic acid was converted into its anhydroxime by treating with hydroxylamine hydrochloride in 80% alcohol solution.[5] It is

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[1] Staudinger, *Die Ketene.*

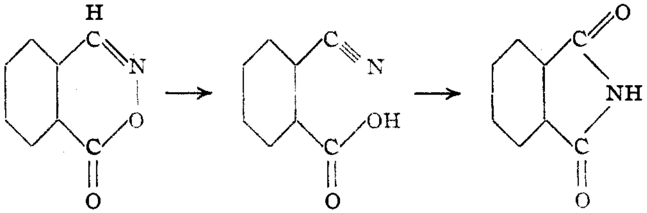
[2] Compare Dunston and Dymond, "On the Reduction of Trimethyl Isoxazole," *J. Chem. Soc.*, 59, 410 (1891).

[3] *Ber.*, 31, 369 (1898).

[4] German patent 79,693.

[5] Allendorf, *Ber.*, 24, 2346 (1891).

a colorless crystalline compound melting at 187°, resolidifying and melting again at 225–228°, the latter being the melting point of phthalimide. When heated cautiously to 145°, it is converted into *o*-cyanobenzoic acid. This behavior will explain the formation of phthalimide during the process of reduction.



Reduction.—4 g. *o*-aldehydo benzoic anhydroxime are dissolved in 10 cc. glacial acetic acid in the cold. An excess (three times theoretical amount) of zinc dust is added in small portions during 20 minutes, the reaction mixture being cooled by water to prevent its reaching a temperature above 50°. This precaution is necessary in order to keep the anhydroxime from passing into phthalimide by internal rearrangement. The reduction proceeds readily and is usually nearly complete by the time all the zinc is added. The mixture is allowed to stand for a half hour, when the liquid above the remaining zinc is poured into cold water (150 cc.), the zinc being washed with a little acetic acid and the washings added to the water. The aqueous solution is then neutralized with a concentrated solution of sodium carbonate until zinc carbonate begins to precipitate out. The mixture is steam distilled and the still residue extracted with ether. The ethereal extract, upon evaporation in a current of dry air, deposits a crystalline mixture of phthalimidine and phthalimide. Separation is effected by extracting with 70% alcohol which dissolves the former but not the phthalimide. The phthalimidine obtained forms long transparent needles,[1] m. p. 150–151°.

The steam distillate obtained as stated above, is extracted with ether; on evaporation small quantities of a colorless oil remain. This liquid was identified as dihydroisoindole.

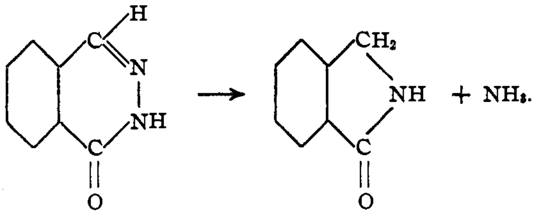
Phthalimidine results from the reduction of phthalimide by tin and hydrochloric acid.[2] It, therefore, appeared possible that the production of this compound under the above conditions was due to a preliminary conversion of the anhydroxime into phthalimide. In order to test this, phthalimide itself was submitted to the action of zinc dust and acetic acid under the above conditions; only traces of phthalimidine were formed.

The reduction of phthalazone by means of tin and hydrochloric acid results in the production of phthalimidine.[3]

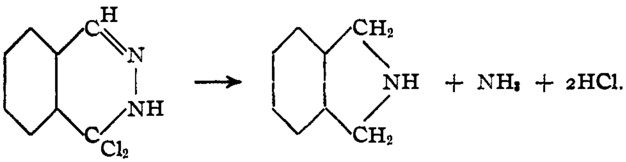
[1] Graebe, *Ann.*, **247**, 291 (1889).

[2] Graebe, *Ber.*, **17**, 2598 (1884).

[3] Gabriel and Neumann, *Ibid.*, **26**, 521 (1893).



But Gabriel and Neumann[1] do not state whether any dihydroisoindole is formed at the same time. The latter compound they obtained by the action of tin and hydrochloric acid on chlorophthalazone.



The method described by us might well be modified to yield satisfactory quantities of dihydroisoindole; it is essentially simpler than that previously employed.

Reduction of *o*-Acetyl Benzoic Anhydroxime.—The necessary *o*-acetyl benzoic acid was prepared according to the method of Gabriel and Michael.[2] The anhydroxime was obtained as described by Gabriel.[3]

Reduction.—5. g. of the anhydroxime are treated with 15 cc. of glacial acetic acid and warmed to promote solution. Between 3 and 4 times the calculated quantity of zinc dust is then added in small portions during a period of 15 or 20 minutes. The heat generated is sufficient to maintain a temperature of about 100°. A few drops of liquid are then poured into water. If this results in turbidity due to the separation of unaltered anhydroxime the reaction is not complete, in which case it is furthered by boiling for a few moments. Usually this is unnecessary. After standing for a half hour the reaction-mixture is treated as described for *o*-aldehydo benzoic anhydroxime.

The product left on evaporating the ethereal extract of the still residue, is 1-methyl phthalimidine as shown by its constants (m. p. 110°).[4] The distillate contains 1-methyl dihydroisoindole. It is left as an oil but soon passes into a crystalline mass if exposed to the air, forming a carbonate.

Acetyl-1-methyl Phthalimidine.—One of us has found that 1-phenylphthalimidine is readily converted into an acetyl derivative.[5] 1-Methyl

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[1] Gabriel and Neumann, *Loc. cit.*

[2] *Ber.*, 10, 1554 (1877).

[3] *Ibid.*, 16, 1995 (1883).

[4] Gabriel and Neumann, *Ibid.*, 26, 705 (1895).

[5] Rose, *Loc. cit.*

phthalimidine behaves in a like manner. If 2 g. are treated with 15 cc. of boiling acetic anhydride and 4 g. of anhydrous potassium acetate, during 1–2 hours, an acetyl derivative is formed. This separates as an oil on pouring the reaction mixture into water. After extraction with ether, it may be recrystallized from aqueous acetone. The compound forms transparent, colorless needles melting at 71°. It is readily soluble in all the ordinary organic solvents.

Reduction of β-Keto Butyric Anhydroxime, or Methyl Isoxazolone.—The anhydroxime is prepared by the action of hydroxylamine on a strongly alkaline solution of acetoacetic ester.[1] The preparation, as noted by Hantzsch, is one very apt to fail. The authors find that it is necessary to keep the temperature at about 70° during the hydrolysis of the oximino ester by barium carbonate and to filter at once when the liquid assumes a deep yellow color. If this precaution is not observed the anhydroxime cannot be isolated.

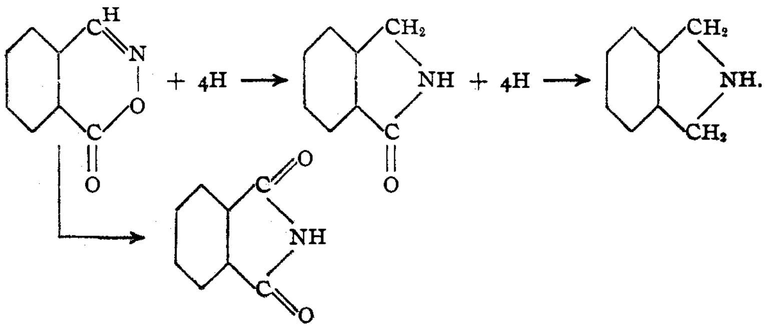
Reduction.—5 g. of the anhydroxime were dissolved in the minimum amount of glacial acetic acid and a large excess of zinc dust added in small portions with constant shaking. On warming, a vigorous reaction took place. After boiling for an hour the mixture was poured into water, neutralized with sodium carbonate and extracted with ether. A thick syrupy mass remained on evaporating the solvent. All attempts to purify this material failed. When extracted with water it yelded a small quantity of zinc butyrate.

The aqueous solution obtained by pouring the reduction mixture into water gave off ammonia on treatment with sodium hydroxide. It would therefore appear that the action of nascent hydrogen converts this anhydroxime into ammonia and the free acid.

Efforts to modify the reaction by substituting milder reducing agents proved futile.

Summary.

(1) The reduction of *o*-aldehydo benzoic anhydroxime by means of zinc



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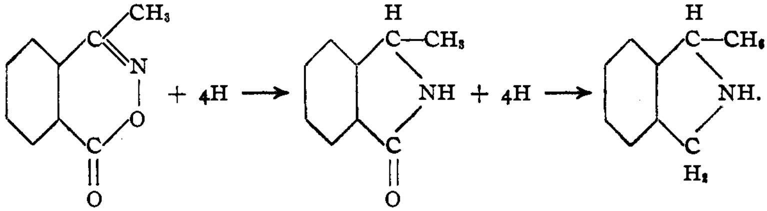
[1] Hantzsch, *Ber.*, 24, 495 (1891).

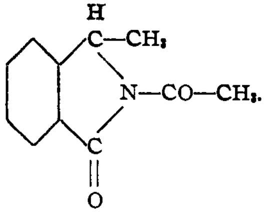
and acetic acid results in the formation of phthalimidine and dihydroisoindole, some phthalimide being produced at the same time by internal rearrangement of the anhydroxime.

(2) The reduction of *o*-acetyl benzoic anhydroxime under like conditions gives 1-methyl phthalimidine and 1-methyl dihydroisoindole.



It does not yield any 1-methyl isoindole even when the action is moderated.

(3) An acetyl derivative of 1-methyl phthalimidine is described.



(4) β-Ketobutyric anhydroxime (methyl isoxazolone) yields ammonia and butyric acid upon reduction in acid media. There is no evidence of the production of a tetratomic ring.

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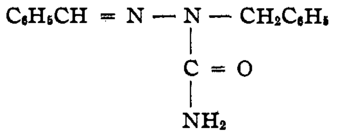
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS.]

THE USE OF CYANIC ACID IN GLACIAL ACETIC ACID. II. THE ADDITION OF CYANIC ACID ON BENZALAZINE.

BY J. R. BAILEY AND N. H. MOORE.

Received September 12, 1916.

Bailey and his co-workers have shown that, in the case of a number of weak nitrogen bases, difficultly soluble in water, carbamide derivatives are readily formed in glacial acetic acid solution by stirring in finely ground potassium cyanate.[1] In this article it is further shown that this modified form of the Woehler synthesis is serviceable in the preparation of benzylideneaminobenzylurea



$$\begin{array}{l} C_6H_5CH = N - \underset{\substack{| \\ C\,=\,O \\ | \\ NH_2}}{N} - CH_2C_6H_5 \end{array}$$

HCNO adds onto benzalbenzylhydrazine, $C_6H_5CH_2NHN = CHC_6H_5$,

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[1] THIS JOURNAL, 37, 940, 1884 (1915); 38, 1784 (1916).