The analyses and the behavior of the reaction indicates that α-methyl-glutaric acid might have been formed, but in quantities too small to be isolated.

Summary

1. When isocampholactone is heated with nitric acid, the two main products formed are nitro-isocampholactone and a lactone acid. This lactone acid gives an amide which on treatment with sodium hypobromite is converted to a keto acid. This, on treatment with methylmagnesium iodide, regenerates isocampholactone and also probably forms a *trans*-hydroxy acid. This series of reactions demonstrates that isocampholactone contains methyl groups in the 1,2,3 positions and should be called the lactone of 3-hydroxy-1,2,3-trimethyl-cyclopentane-carboxylic acid.

2. A possible explanation of the isomerism of campholactone and isocampholactone is given.

3. Nitro-isocampholactone on treatment with alkali gives almost quantitatively acetone and a nitro acid of 6 carbon atoms. The nitro group in this acid is secondary, as proved by the nitrous acid test and by the formation of a sodium salt of the enolic form of the nitro group in both the acid and its ester. This test proves that it is a cyclobutane derivative and should be called 2-nitro-1-methyl-cyclobutane-carboxylic acid.

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SIMPLIFICATION OF THE GATTERMANN SYNTHESIS OF HYDROXY ALDEHYDES

BY ROGER ADAMS AND I. LEVINE[1]

The Gattermann synthesis of hydroxy aldehydes[2] which consists in saturating an anhydrous ether solution of certain phenols and anhydrous hydrogen cyanide with dry hydrogen chloride, sometimes with the addition of anhydrous zinc chloride, gives excellent yields of products which are readily purified. The method has proved to be invaluable for the preparation of certain intermediates in the synthesis of many natural compounds, and is still the only available process for preparing many representative hydroxy aldehydes. In spite of the ease with which the reaction generally takes place, its use in the laboratory is not as frequent as might be expected. This is due to the necessity of using anhydrous hydrogen cyanide, a product the preparation and handling of which in-

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[2] Gattermann, *Ber.*, **31**, 1765 (1898); **32**, 278, 284 (1899); *Ann.*, **357**, 313 (1907). Morgan and Vining, *J. Chem. Soc.*, **119**, 177 (1921).

volve many disagreeable features. More recently,[3] this method of prep-
aration of the hydroxy aldehydes has been simplified somewhat by the
generation of the hydrogen cyanide and its direct addition to the reaction
mixture. Even this procedure does not make the preparation safe for
any but the more experienced investigator. Such reactions as the Gatter-
mann synthesis, involving anhydrous hydrogen cyanide, are consequently
limited in their use.

Recently Karrer[4] has shown that bromocyanogen may be substituted for hydrogen
cyanide in the preparation of certain hydroxy aldehydes. The yields, however, do not
appear to be as satisfactory as when hydrogen cyanide is used.[3b] Bromocyanogen is more
conveniently made in the laboratory and more easily handled than anhydrous hydro-
gen cyanide, but even this product is extremely poisonous and much care must be used.
Moreover, only a freshly prepared sample of bromocyanogen gives satisfactory results.

This research had as its object the modification of the Gattermann
synthesis in such a way as to avoid using anhydrous hydrogen cyanide.
Experiments in which hydrogen cyanide was replaced by certain of its
salts have been carried out. Of these various salts, zinc cyanide would
seem the most promising choice, since it would be changed during the
reaction into a mixture of zinc chloride and hydrogen cyanide. Zinc
chloride has already been shown by Gattermann to be an effective condens-
ing agent for the reaction of the hydrogen cyanide with certain phenols
in the presence of hydrogen chloride. The laboratory results have fully
met the expectations. Very satisfactory yields have been obtained with
resorcinol, α-naphthol, β-naphthol, orcinol and pyrogallol; in fact, the
yields were similar to those obtained with anhydrous hydrogen cyanide.
Undoubtedly any phenol that can be converted to an hydroxy aldehyde
using the directions of Gattermann can be converted to an hydroxy alde-
hyde equally well by this slight but most convenient modification.

The preparation of zinc cyanide suitable for use in the reaction described
above proved to be a problem in itself. Up to the present time zinc cyan-
ide free from zinc oxycyanide has been made by the action of hydrogen
cyanide upon zinc oxide or by other methods entirely unfitted for the pres-
ent problem, the success of which depends upon the ease of preparation
of the zinc cyanide. An easy method for preparing a satisfactory zinc
cyanide for the Gattermann reaction was finally found. It consisted in
treating an aqueous solution of sodium cyanide with magnesium chloride
in order to precipitate the impurities of sodium hydroxide and sodium
carbonate. Zinc cyanide was then precipitated by adding to the solution
a molecularly equivalent amount of zinc chloride in alcohol. The product
obtained is about 90% zinc cyanide and contains no impurity that inter-
feres with the Gattermann synthesis.

[3](a) Ziegler, Ber., 54B, 110 (1921). (b) Johnson and Lane, THIS JOURNAL, 43,
354 (1921).
[4] Karrer, Helvetica Chim. Acta, 2, 89 (1919).

The literature reports that zinc cyanide gradually decomposes on stand-ing. The product made as described, if kept in a dry atmosphere, appar-ently decomposes only very slowly. After several weeks it was analyzed and showed a depreciation of about 2%. Nevertheless, it gave just as satisfactory results as when first prepared. No extensive experiments were made to determine just how long the zinc cyanide could be kept, since it can be so easily and quickly prepared.

Gattermann has also described the preparation of aldehydes from phenol ethers by the action of hydrogen chloride, hydrogen cyanide and anhydrous aluminum chloride on phenol ethers. Moreover, he has shown that certain hydroxy aldehydes which could not be made by the direct condensation of the phenol with hydrogen cyanide, hydrogen chloride and zinc chloride could be formed by the action of hydrogen chloride, hydrogen cyanide and anhydrous aluminum chloride upon the phenol. A modifi-cation of these last processes in such a way as to avoid the anhydrous hydrogen cyanide has proved successful and is now being studied in detail.

The authors are indebted to Dr. J. H. Reedy for suggestions in connec-tion with the purification of the zinc cyanide.

Experimental Part

Zinc Cyanide.—To a 5% excess over 1 molecular equivalent of technical sodium cyanide calculated as 100% pure, regardless of its purity, dissolved in about 25% more than an equal weight of water, was added magnesium chloride solution until no more pre-cipitate of magnesium hydroxide and carbonate formed (this requires an amount of magnesium chloride sufficient to precipitate a quantity of sodium carbonate equal in weight to about 7–8% of the sodium cyanide used). The precipitate was filtered off immediately and the filtrate added at once to 1 molecular equivalent of zinc chloride dissolved in as small an amount as possible of 50% alcohol. The zinc cyanide precipitated and was filtered off. When the magnesium hydroxide and carbonate were not removed immediately and the zinc cyanide precipitated at once, the reaction mixture turned dark until finally it became almost black. When the zinc chloride was added to such a colored solution the zinc cyanide formed was always colored. The zinc cyanide was washed on the filter with alcohol, then with ether and dried in a desiccator or in an air-bath at 50°.

The only important precaution in this preparation is to insure an excess of zinc chloride over sodium cyanide. If the sodium cyanide is in excess, the zinc cyanide invariably precipitates as a sticky mass which is difficult to filter and unsatisfactory for the preparation of the hydroxy aldehydes.

The product was analyzed for the amount of cyanide present by titrating it with standardized silver nitrate solution, and was shown to be about 90% pure zinc cyanide. The remaining 10% was presumably for the most part sodium chloride, with small amounts of zinc chloride, magnesium chloride and perhaps traces of basic zinc cyanide. These do not interfere with the Gattermann reaction.

General Method of Preparation of the Hydroxy Aldehydes.—A 500cc. wide-mouth bottle was fitted with a stopper holding an efficient mechanical stirrer with a mercury seal, a reflux water condenser and an inlet tube, with wide mouth to prevent clogging from the precipitate, ex-

tending nearly to the bottom of the bottle. To this inlet tube was attached a safety bottle and to this a generator producing dry hydrogen chloride. To the top of the condenser was connected a tube leading into a wash bottle containing sulfuric acid; from this a tube was led to a safety bottle and from the latter a tube to the surface of a sodium hydroxide solution.

In the reaction bottle was placed 20 g. of the hydroxy compound in 150 to 200 cc. of dry ether. Sufficient dry zinc cyanide was then added, equivalent to 1.5 mol. for every mol. of phenol. The mechanical stirrer was started and dry hydrogen chloride was passed in rapidly. The zinc cyanide gradually disappeared with the formation of a milky solution (the milkiness being probably due to the sodium chloride present) and as more and more hydrogen chloride dissolved, the imide hydrochloride condensation product began to separate as a thick oil. In 10 to 30 minutes this oil turned to a solid. At the end of about 1.5 hours the ether was usually saturated with hydrogen chloride. When this point was reached, the stream of gas was passed in more slowly and stirring was continued for $1/2$ hour longer to be certain that all the phenol had reacted. The ether was decanted from the solid material and the imide hydrochloride then decomposed with water or dil. alcohol as described below.

The amount of ether used in the above reaction was somewhat greater than that suggested by Gattermann. It was found, however, that the colored by-products which invariably formed with these phenolic compounds were smaller in amount the larger the amount of solvent.

It was also possible to use dry chloroform in place of dry ether. Under these conditions the reaction went practically the same, but the crude products were somewhat more colored.

Resorcyl Aldehyde.—With resorcinol the reaction mixture turned pink and the solid material tended to be pink. Previous investigators advised the decomposition of the imide hydrochloride by boiling it with water for about 5 minutes and then allowing the product to cool. It was found that by this procedure the resorcyl aldehyde which separated amounted to about 70% of the calculated amount. It was found to be much more satisfactory to add about 100 cc. of water to the imide hydrochloride, raise the solution to the boiling point, filter the mixture and then immediately allow the filtrate to cool. In this way about a 50% yield of aldehyde was obtained. This was filtered and the filtrate was allowed to stand. In about 10 to 15 hours, more material separated which, upon filtration, amounted to about 45% of the calculated yield, giving a combined yield of 95%.

The resorcyl aldehyde obtained had only the slightest tinge of color and melted very sharply at 135–136° (Gattermann, 136°). By recrystallization from water with the addition of boneblack, a product absolutely free from traces of colored by-products was produced.

Orcinol Aldehyde.—The orcinol used in these experiments must be thoroughly dried to remove the water of crystallization which is ordinarily present. The reaction proceeded smoothly with the development of a pink color. No special precaution was necessary in the decomposition of the imide hydrochloride. It was merely boiled for

two to three minutes with 100 cc. of water, filtered and allowed to cool. The yield of product was about 85%; m. p., 178–180° (Gattermann, 180°). By a crystallization from water with the addition of boneblack a very pure product was obtained.

β-Naphthol Aldehyde.—The imide hydrochloride was decomposed by boiling it with 100 cc. of water and an 85% yield of product was obtained, melting a few degrees below the correct point. After recrystallization from water with the addition of bone-black, a very pure product melting at 80–81° (Gattermann, 81°) was obtained.

α-Naphthol Aldehyde.—In contrast to the hydroxy compounds described above where the reaction mixture was pink, that from α-naphthol became deep yellow. The imide hydrochloride was decomposed by boiling it with 700 cc. of 30% alcohol until complete solution took place; then the solution was filtered and allowed to cool. When water was used in this experiment, the α-naphthol aldehyde, because of its insolubility in water, tended to separate immediately and to prevent the smooth and complete de-composition of the imide hydrochloride. The product obtained as described formed in 72% yield and melted slightly low. More aldehyde could be recovered from the mother liquor. By recrystallization from water or 30% alcohol with added boneblack a very pure product resulted; m. p., 178° (Gattermann, 180°).

Pyrogallol Aldehyde.—The ether in the reaction mixture turned more deeply colored than when the other phenols were used, but the imide hydrochloride was light colored. It was decomposed by boiling it for two to three minutes with 400 cc. of water. The yield was about 45%, and the product melted at 158° (Gattermann, 158°). It can be obtained very pure by recrystallization from water containing boneblack.

Summary

1. Gattermann found that certain types of phenols condensed with hydrogen chloride, hydrogen cyanide and anhydrous zinc chloride to give compounds that hydrolyzed readily to form hydroxy aldehydes. A de-scription of a method is given by which these same aldehydes can be formed in the same yields as found by Gattermann, but zinc cyanide is substi-tuted for the anhydrous zinc chloride and hydrogen cyanide that he used.

2. Anhydrous zinc cyanide for this reaction was produced by treating aqueous sodium cyanide with magnesium chloride to precipitate the im-purities of carbonate and hydroxide, filtering the precipitate and adding alcoholic zinc chloride to the filtrate.

URBANA, ILLINOIS