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## Experiments on the Keto-cleavage of D1 (2-cyanoethyl) Acetoacetic Ester

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EXPERIMENTS ON THE KETO-CLEAVAGE

OF

D<sub>1</sub> (2-CYANOETHYL) ACETOACETIC ESTER

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Submitted as Partial Fulfillment  
of Senior Honors Work in  
Chemistry

By: Charles W. Huff, Class of 1946.

Approved By:

Russell D. Slings.

Experiments on the Keto-cleavage of -Di(2-cyanoethyl) acetoacetic ester.  
by E. F. Riener and C. W. Huff

The inspiration for this research was derived from the work of Bruson and Riener who discovered the reaction involving the addition of acrylonitrile to certain compounds containing activated hydrogen atoms. In the course of their researches they found that many various groups or radicals caused this activation. Some of these are the nitrile group, the ketone group and the aldehyde group. In effect this property of acrylonitrile, heretofore undiscovered, allowed for the cyanoethylation of many different compounds and provided a means of adding a three carbon atom chain to many substances thus providing a valuable building block for many synthetic procedures. Never before had this been possible on such a large scale over such a large spectrum of compounds. Heretofore this particular type of synthetic addition had been possible only through such costly and inefficient procedures as the addition of halogenated derivatives of compounds to sodium derivatives of other compounds. Not only was this procedure costly but the number of compounds allowing this sodium addition was relatively few compared with the large number of cyanoethylation reactions made possible by the new method.

The basis for our research was founded on the addition of acrylonitrile to two substances, malonic ester and acetoacetic ester, particularly the latter. The actual addition of acrylonitrile to these compounds and the proof of their structures along with the establishing of certain of their physical constants had already been accomplished by Bruson and Riener. Our work was based on two very interesting reactions which could possibly occur on the hydrolysis of the addition compound of aceto-acetic ester. These possibilities hinge on the keto or acid cleavage of the acetoacetic ester addition compound and the degree of hydrolysis of both the addition compound of acetoacetic ester and malonic ester. The malonic ester compound was to serve merely as a comparator compound for purposes of structure proof.



That many possibilities exist for this research is evidenced by the fact that it is theoretically possible to obtain some thirty different different compounds from the single hydrolysis of the addition product of acetoacetic ester alone. These compounds are represented by all the permutations and combinations which might result from either or both of the two types of cleavage and the formation of the carboxyl group, the acid amide group, and/or the nitrile group at the end of the cyanoethyl addition chain. Our work involved the control of this hydrolysis by such procedures as varying the concentration of the hydrolytic agent (be it acid or base), varying the temperature, varying the time of reaction, and varying the concentration of the substance to hydrolysed. Having attained certain of these compounds resulting from this hydrolysis, there are yet many other possibilities for further research and development which manifest themselves. If the compound be a nitrile it is possible that it could be hydrogenated to the amine and subsequently dehydrated, undergoing an internal combination in such a manner as to form a substituted piperadine derivative, a compound related to the medically important pyridine series of which sulfapyridine is perhaps the most widely known. If the compound were a dibasic acid it is theoretically possible to form its anhydride and on later heating above its melting point to decarboxylate the compound thus forming a substituted cyclohexanone derivative with the substitution group in the para position to the ketone radical. It is interesting to note that Perkin in his researches in which he synthesized many of the members of the terpene series used just such a para substituted compound as a cornerstone so to speak. Another possibility along this line which might prove fruitful would be the cyanoethylation of acetyl acetone and on subsequent treatment with a mild hydrolytic agent in such a manner as to cause fission, the derivation of compounds of the gamma acetyl pimelic acid type, perhaps by a much more direct and efficient method than that involved in the cyanoethylation and



### 3- Experiments on Keto-cleavage(cont.)

cyanoethylation and hydrolysis of the acetoacetic ester. It is well to note here, however, that an attempt was made to cyanoethylate this compound by Bruson and Riener and they found no trace of the hoped for di-cyanoethyl acetyl acetone in the reaction mixture. Notwithstanding this fact, it is yet possible that some means may be found to cause this reaction to occur, since the very great number of compounds on which they were obliged to try their newly found reaction made brevity, of necessity, an absolute must. Other variations of the above theories and the elaboration of new ones would doubtless become evident as the research along these lines progressed.

When this work was begun a review of the literature revealed that little work had been done on the compounds of the gamma substituted pimelic acid series. Of special interest was the work done by William Henry Perkin, jun., and John Lionel Simonsen at the University of Manchester in England. They prepared gamma acetyl pimelic acid in the course of their experiments while attempting to synthesize nopinone, a ketone of great interest which Baeyer (Ber. 1896, 29, 22, 25) first obtained during the course of his classical researches on the products resulting from the oxidation of the oil of turpentine. The experiments which they carried out may be briefly summarized as follows.

The sodium derivative of alpha acetyl ethyl glutarate was treated, in alcoholic solution with ethyl beta-iodopropionate, when interaction rapidly took place with the formation of ethyl gamma-acetyl pentane-alpha-gamma-omega tricarboxylate, and this ester, when digested with ~~hydro~~ hydrochloric acid, was readily decomposed and converted into gamma-acetyl pimelic acid. When ethyl gamma-acetyl pimelate is treated with magnesium methyl iodide, it is converted into the lactone of ethyl ~~hydro~~ hydrogen gamma-isopropenol pimelate, and this lactone reacts readily with hydrobromic acid with the formation of an oil, which on esterification yields ethyl gamma-(bromoisopropyl) pimelate.



4- Experiments on Keto-cleavage(cont.)

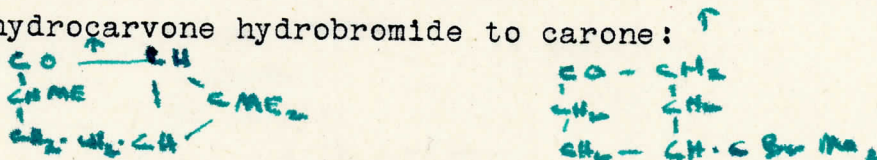
When this bromo-ester is digested with pyridine, it is decomposed with elimination of hydrogen bromide and formation of ethyl gamma-isopropylidene pimelate, which, on hydrolysis, yields gamma-isopropylidene pimelic acid, the constitution of which is proved by the fact that, on oxidation with permanganate and then with chromic acid, it yields acetone and succinic acid. The solution of ethyl gamma-isopropylidene pimelate in toluene reacts readily with sodium and yields ethyl 4-isopropylidene cyclohexanone-2-carboxylate, an oil which decomposes on distillation and the alcoholic solution of which gives an intense violet coloration with ferric chloride.

This ketonic ester is readily hydrolysed by alcoholic potash, and one of the products of hydrolysis is 4-isopropylidene cyclohexanone, which distills at 219-221 degrees centigrade, yields a semicarbazone of melting point 201 degrees, and is isomeric with nopinone, camphenilone, sabinenone, and with other important ketones of the camphor and terpene series.

4-isopropylidene cyclohexanone combines readily with hydrogen bromide with formation of 4-beta-bromoisopropylcyclohexanone, and if the formula of this substance be written side by side with that of nopinone,



it will be seen at once that these substances are related in the same way as dihydrocarvone hydrobromide to carone:



Now Baeyer (Ber., 1894, 27, 1919; 1896, 29, 6) has shown that carone is formed when dihydrocarvone hydrobromide is left in contact with an alcoholic potash at 0 degrees, and, in order to bring about the similar conversion of 4-beta-bromoisopropylcyclohexanone into nopinone,



this bromo-compound was caused to react with alcoholic potash under a variety of conditions, but were unable to detect the formation of even traces of nopinone. In every case the elimination of hydrogen bromide appeared to proceed in the direction:



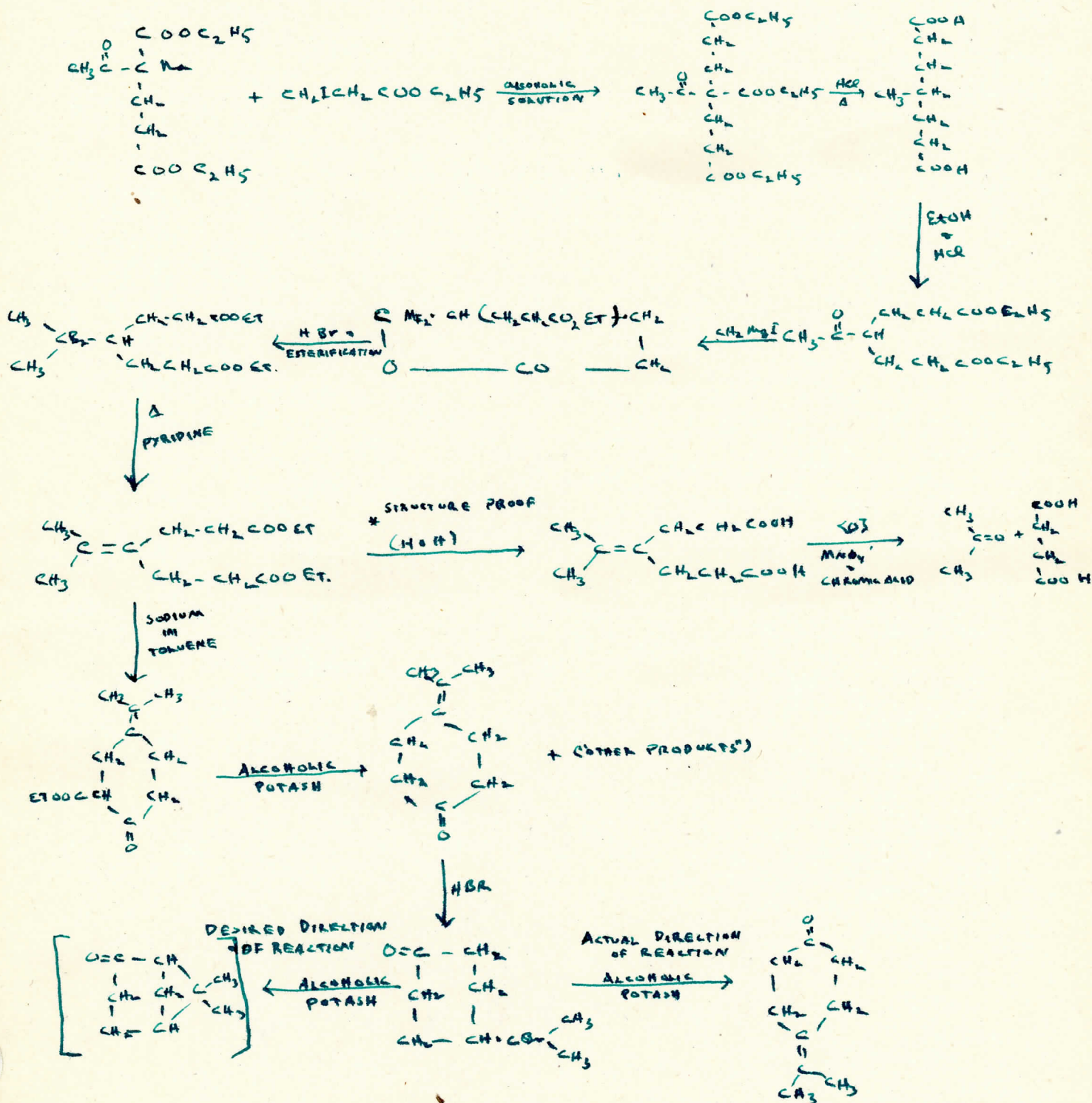
giving rise to the formation of 4-isopropylidenecyclohexanone.

Next the hydrogen bromide additive compound of ethyl 4-isopropylidenecyclohexanone-2-carboxylate, a substance capable of yielding a sodium derivative which might reasonably be expected to undergo internal condensation with elimination of sodium bromide and formation of ethyl nopinone carboxylate, was prepared. Although elimination of sodium bromide did take place when the sodium derivative was digested in alcoholic solution, the product of reaction, on hydrolysis with dilute alcoholic potash, did not furnish a trace of nopinone. In previous communication (Trans., 1907, 85, 817), the fact was referred to that the ~~cyclopropane~~ cyclopropane ring is not infrequently produced with much greater ease than the cyclobutane ring." Despite this apparent lack of success it is desirable to note here the closing paragraph of Perkin and Simonsen's paper, "One of the principal difficulties which we had to deal with in the above experiments was the impossibility of obtaining ethyl 4-isopropylidene cyclohexanone-2-carboxylate, and especially 4-isopropylidenecyclohexanone in sufficient quantities for detailed investigation. Owing to the very large quantities of ethyl beta-iodopropionate required, the preparation of these substances is very costly, and, in spite of a large number of comparative experiments, the yield was always very small. Possibly, when better methods of preparation are available, it may still be ~~possible~~ found possible to carry out a synthesis of nopinone on the lines indicated above." From this last it would seem to indicate that if our method of preparation of gamma-acetyl pimelic ~~acid~~

6- Experiments on Keto-cleavage(cont.)

acid proves to be practical, it is a distinct possibility that this synthesis of nopinone might be taken up where Perkin and Simonsen left off and carried to a successful conclusion.

Following is the scheme of reactions involved in the above attempted synthesis.





7- Experiments on Keto-cleavage(cont.)

When this research was begun it was hoped that we would be able to synthesize gamma-acetyl pimelic acid. The many possibilities for the various degrees and directions which this reaction may take have been previously indicated. Following is a ~~brief~~ resume of the various experiments which were performed with the production of apparently new compounds. It cannot be definitely stated as yet, however, that these are new compounds as these experiments still await analysis for verification. The experimental procedure is also given together with a bibliography of the pertinent literature examined and a scheme of possible reactions.

The first attempt was to use a 5% solution of sodium hydroxide which it was hoped would perform the desired cleavage under reflux. The resulting compound (I) was a white crystalline one which melted at 112-114 degrees centigrade. It was thought that acid cleavage had occurred and that compound (I) was gamma-carboxyl pimelic acid instead of the hoped for gamma acetyl pimelic acid.

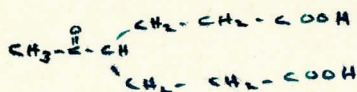
The second method was to use sodium carbonate for the cleavage in hopes that its weaker action would effect the desired result. From this attempt was derived a white crystalline compound melting at 122 degrees centigrade. It was thought that this compound might be gamma-acetyl pimelionitrile. Some of this compound (II) was further hydrolyzed and a slightly viscous yellow oil resulted, but due to lack of time this experiment was never pressed further.

The third method was to reflux the di-cyanoethyl addition compounds with concd. HCl. From this experiment resulted two compounds: (III-A) a viscous yellow syrup which was distilled under reduced pressure, and (III-B), a white crystalline compound which could not be induced to melt even at 300 degrees centigrade. It was believed that compound (III-A) was the desired gamma-acetyl pimelic acid and that compound (III-B) could possibly be gamma-acetyl pimelamide or some other intermediate derivative of gamma-acetyl pimelic acid.



8- Experiments on Keto-cleavage(cont.)

Attempt to prepare gamma-acetyl pimelic acid:



Used: 45gms.....Dicyanoethyl acetoacetic ester

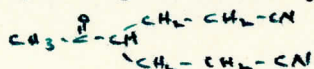
45gms.....NaOH in 900cc H<sub>2</sub>O (5%)

Refluxed above on oil bath for three hours. Cooled and acidified to Congo Red with HCl. Evaporated on steam bath in vacuo. Extracted residue with acetone and evaporated this off on steam bath. The residue was a brown oil which crystallized completely on standing in air.

Sucked as dry as possible on Buchner funnel. 27 gms. of brownish crystalline material remained. MP-111 to 113 degrees centigrade.

Recrystallized twice from nitromethane. This product obtained as small white needle-like crystals melted at 112-114 degrees centigrade.

Attempt to prepare gamma-acetyl pimelionitrile



Used: 150gms.....Dicyanoethyl acetoacetic ester

147 gms Na<sub>2</sub>CO<sub>3</sub>H<sub>2</sub>O in 1300cc H<sub>2</sub>O (10%)

Refluxed above till all oil dissolved. Cooled. Acidified to Congo Red with HCl. Dried in vacuo. Washed salt with hot ethanol.

Filtered and washed residue with hot ethanol. Filtered. Dried down filtrate on steam bath in vacuo. Oily residue from drying down weighed 84gms.

Distilled under reduced pressure.

1. 195°-205°-1-2mm-~~36.5gms~~ 2.5gms.
2. 205°--(213°-222°)--1.2mm-36.5gms.
3. 222°--(225°-232°)-254°-1-3mm-36.0gm

Residue---9gm.

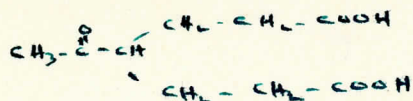
Recrystallized cut # 3 first from ethanol with norite. (MP 116°-117°)

Then three more times from water using norite the first two.(MP122°)



9- Experiments on Keto-cleavage(cont.)

Attempt to prepare gamma-acetyl pimelic acid



Used: A       gms.....Dicyanoethyl acetoacetic ester.

B       cc.....HCl in cc H<sub>2</sub>O.

B was added to A and both were refluxed for four hours over an oil bath. It was then diluted with 200cc H<sub>2</sub>O and heated under reflux for eight more hours. Evaporated down on a steam bath in vacuo. A crystalline material (B) separated out and was filtered off. This crystalline material was recrystallized from large amounts of EtOH in which it is slightly soluble. (It is ~~slightly~~ soluble in water, and either VSS or IS in ether, benzene, ethyl acetate, N-Butyl bromide, N-butyl alcohol, acetone, nitroethane, and 2-nitropropane and is soluble in glacial acetic acid. Wt. of crystalline material 16.8gms.

The residue was dried down the rest of the way and remains as a thick viscous yellow syrup, (A), which refused to crystallize on exposure to air for several days. Wt. 62.6gms. Syrup was distilled in vacuo.

<u>Pressure</u>	<u>Cut #</u>	<u>Temperature</u>	<u>Wt. of Cut</u>
5-mm	1	215°-235°	11.7 gm
4mm	2	235°-265°	29.7 gm
4-15mm	3	265°-270°	9.5gm
		Residue.....	<u>9.3gm</u>
		Total.....	<u>60.2gm</u>





Bibliography

Bruson and Riener, Journal Am. Chem. Soc., 64, 2858 (1942)

Beilstein, gamma-acetyl pimelic acid  $C_9H_{14}O_5$

A method for preparation of nitriles from aldehydes  
p4517, vol 52, No 11 Journal Am. Chem. Soc.-1930

Prepn. of nitriles by dehydration of amides  
p399, Vol 36, No 1, Chemical Abstracts 1942

Rosenmund von Braun Nitrile Synthesis  
p756 vol 36, No 1, Chemical Abstracts 1941

Purification of Nitriles  
p6980, vol 35, No 2, CA 1941

Acrylonitrile plus 1-3 butadiene  
p1069, vol 35, No 1, CA 1941

Prepn. of nitriles of lower aliphatic acids  
p2906, vol 35, CA 1941

Aliphatic amino nitriles  
p 139, vol 35, CA 1941

Nitriles of acrylic acid  
p 139, vol 35, CA 1941

Methacrylonitrile  
p139, vol 35, CA 1941

Nitriles  
p 139 vol 35 CA 1941

Nitriles  
p1049, vol 36, CA 1942

Trichloroacetonitrile  
p1049, vol 36, CA 1942

Adipin nitrile  
p1049, vol 36, CA 1942

Nitriles  
p1335, vol 36, CA 1942

Aliphatic carboxylic acid nitriles  
p1335, vol 36, CA 1942

Carboxylic acid nitriles  
p1335 vol 36, CA 1942

Carbocyclic compounds plus acrylonitrile  
p 5188, vol 36, CA 1942

Unsaturated nitriles  
p778, vol 34 CA 1940

Bibliography(cont.)

Introduction of nitrile group  
p1314, vol 34, CA 1940

Preparation of nitriles(Friedel-Crafts reaction)  
p6218, vol 34, CA 1940

Nitriles-phosgene plus a primary amide with 8 C atoms  
p178 vol 33, CA 1939

Aliphatic carboxylic acid nitriles  
p6874, vol 33, CA 1939

Amino nitriles  
p2913, vol 33, CA 1939

Carbonitriles  
p2913, vol 33, CA 1939

Nitriles  
p956, vol 32, CA 1938

Nitriles of 6 C atoms from aliphatic acids  
p770, vol 31, CA 1937

Methyl vinyl ketone plus HCN  
p6668, vol 32, CA 1938

Aliphatic ethers plus HCN  
p115, vol 31, CA 1937

Unsaturation of nitriles in the vapor form  
p2991, vol 30 CA 1936

Nitriles of 10 carbon atoms  
p2991, vol 30, CA 1936

Reaction of Nitriles with  $\text{BF}_3$   
p5756, vol 30, CA 1936