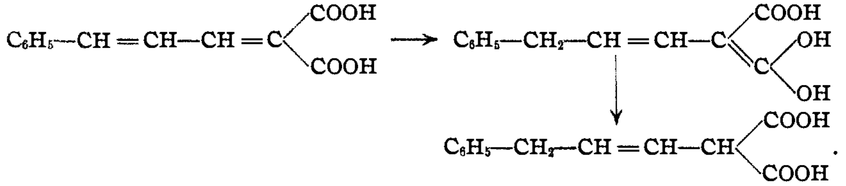
SOME FACTORS BEARING UPON 1,6-ADDITION.[1]

By Tenney L. Davis.

Received May 7, 1919.

That 1,6-addition sometimes takes place has been demonstrated by Straus,[2] who showed that, in the dichloride which is formed when cinnamylidene-acetophenone is treated with phosphorus pentachloride, the two chlorine atoms are in the 1,6-positions with reference to one another. Cinnamylidene-malonic acid when treated with sodium amalgam takes up two hydrogen atoms, and the compound which is formed has been shown by Riiber[3] to be 1,4-hydrocinnamylidene-malonic acid. Its formation is probably due to primary addition of hydrogen in the 1,6-positions and subsequent rearrangement of the product—just as the reduction of cinnamic acid under similar conditions is probably due to 1,4-addition.



$$C_6H_5{-}CH{=}CH{-}CH{=}C\begin{matrix}\diagup COOH\\ \diagdown COOH\end{matrix} \longrightarrow C_6H_5{-}CH_2{-}CH{=}CH{-}C\begin{matrix}\diagup COOH\\ \diagdown\!\!\diagdown C\begin{matrix}\diagup OH\\ \diagdown OH\end{matrix}\end{matrix}$$

$$\downarrow$$

$$C_6H_5{-}CH_2{-}CH{=}CH{-}CH\begin{matrix}\diagup COOH\\ \diagdown COOH\end{matrix}.$$

The interesting question arises whether 1,6-addition will take place in a similar manner with a substance which lacks the middle one of the 3 unsaturated linkages that go to make up the 1,6-conjugated system.

The 1,4-hydrocinnamylidene-malonic acid, which is the immediate product of the reduction, has been shown by Riiber to undergo slow rearrangement into the 3,4-compound, which is evidently more stable. Moreover, Hinrichsen and Triepel[4] found that the primary addition product of bromine and cinnamylidene-malonic ester is the 3,4-compound—in the case where 1,6- or 1,4-addition with the carbonyl group involved was impossible or altogether unlikely, with bromine.

Thiele and Meisenheimer have found that hydrocyanic acid adds to cinnamylidene-malonic ester in the α,β-positions instead of in the α,δ-positions as they expected.[5] This addition, however, is probably not 1,2-addition to the unsaturated linkage, but, in view of the comport-

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[1] An abstract of part of a thesis submitted to the Division of Chemistry of Harvard University in fulfilment of the requirements for the degree of Doctor of Philosophy, June 1917. The research was suggested by Professor Elmer P. Kohler and was carried out at the University of California where I was a guest. Grateful acknowledgment is hereby made to Prof. Kohler for helpful advice and to the University of California for laboratory facilities.—T. L. D.

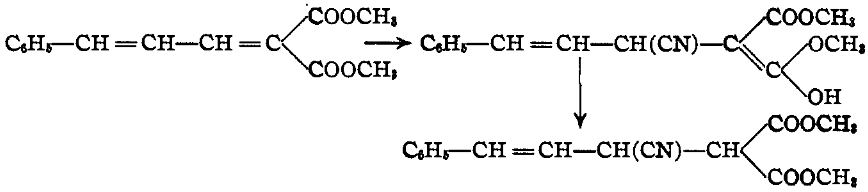
[2] Straus, *Ann.*, 370, 315 (1909).

[3] Riiber, *Ber.*, 35, 2311 (1902).

[4] Hinrichsen and Triepel, *Ann.*, 335, 196 (1904).

[5] Thiele and Meisenheimer, *Ibid.*, 306, 247 (1899).

ment of this compound with the Grignard reagent, is probably 1,4-addition where the carbonyl group is involved.



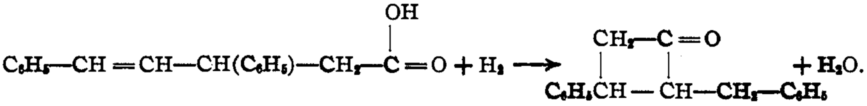
$$C_6H_5—CH=CH—CH=C(COOCH_3)_2 \longrightarrow C_6H_5—CH=CH—CH(CN)—C(COOCH_3)=C(OCH_3)(OH) \longrightarrow C_6H_5—CH=CH—CH(CN)—CH(COOCH_3)_2$$

E. P. Kohler and Miss Marie Reimer[1] and their co-workers have found that cinnamylidenemalonic ester, α-methyl and α-cyan-cinnamylideneacetic ester, and other analogous compounds which contain a 1,6-conjugated system, combine with the Grignard reagent in the 1,4-positions, the 5,6-unsaturated linkage being unaffected. They also react 1,2-, the carbonyl group being involved and the alkoxyl group being replaced by the hydrocarbon residue which is in combination with the magnesium, the relative amounts of 1,2- and of 1,4-addition depending in these cases upon the relative rates at which the Grignard reagent combines with the 1,2- and with the 1,4-systems.

It seemed of interest to examine by experiment whether 1,6-addition could be made to take place in a compound in which the possibility of 1,4-addition was eliminated by the lack of the unsaturated linkage in the 3,4-position.

Barbier[2] experimented with one such compound. By allowing natural methyl-heptenone to react with methyl iodide in the presence of metallic magnesium, he obtained 2,6-dimethyl-heptene-2 ol-6, indicating that with that substance only the carbonyl group is involved when it reacts with methylmagnesium iodide.

In the present investigation 2,4-diphenyl-butene-3 acid-1 was synthesized. This substance differs from similar substances which have been found to enter into 1,6-addition reactions by the lack of an unsaturated linkage in the 3,4-position; and, if it were to combine 1,6- with hydrogen, the carbon atoms occupying the 2- and 5-positions would become linked directly to one another, and the resulting cyclobutane derivative, having two hydroxyl groups on the same carbon atom, would lose water to form a ketone—which could be easily identified by its properties.



$$C_6H_5—CH=CH—CH(C_6H_5)—CH_2—C(OH)=O + H_2 \longrightarrow \begin{array}{l} CH_2—C=O \\ |\qquad\; | \\ C_6H_5CH—CH—CH_2—C_6H_5 \end{array} + H_2O.$$

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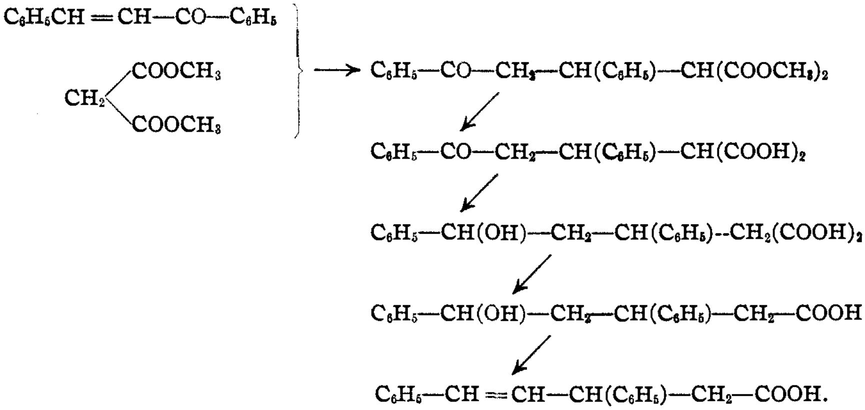
[1] Kohler and Reimer, *Am. Chem. J.*, 33, 333 (1905); Reimer, *Ibid.*, 38, 227 (1907); Reimer and Reynolds, *Ibid.*, 40, 428 (1908); 48, 206 (1912); Reynolds, *Ibid.*, 46, 198 (1911).

[2] Barbier, *Compt. rend.*, 128, 110 (1899).

It was found, however, that the acid is not reduced when boiled with zinc dust and acetic acid, or when its sodium salt in aqueous solution was treated with sodium amalgam. It reacts with phenyl-magnesium bromide to form an unsaturated tertiary alcohol. This substance, therefore, in its comportment toward nascent hydrogen and toward the Grignard reagent, reacts differently from substances similar to it but differing from it by having an unsaturated linkage in the α,β-position, its γ,δ-unsaturated linkage not being affected by either of these reagents; and the results indicate that a 3,4-unsaturated linkage is somehow a necessary factor for the accomplishment of 1,6-addition.

Experimental Part.

2,4-Diphenyl-butene-3 acid-1 was prepared by hydrolyzing the addition product of malonic ester and benzal-acetophenone, by reducing the δ-ketonic acid so obtained, and by splitting off water and carbon dioxide from the resulting hydroxy acid.



Benzal-acetophenone was condensed with methyl and with ethyl malonate by the method recommended by Kohler.[1] The ketone was boiled under reflux for half an hour with about its own weight of absolute alcohol, slightly more than one equivalent of malonic ester, and enough sodium alcoholate to give the solution an alkaline reaction to litmus. The mixture was cooled at once at the tap, and seeded. The crystals which separated were filtered off and washed, and a second crop of crystals was obtained from the mixture after it had been allowed to stand overnight. The yields were good—about 80% of the calculated quantity.

The 2,4-diphenyl-butanone-4 diacid-1,1 methyl or ethyl ester hydrolyzes readily. It was dissolved in warm alcohol and twice the equivalent quantity of potassium hydroxide in a small quantity of water was added while the mixture was shaken. When the alkali was added, the colorless

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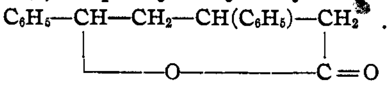
[1] Kohler, *Am. Chem. J.*, 46, 474 (1911).

solution instantly took on a yellow or orange color, and, after a moment's shaking, set to a stiff, pasty mass of crystals. It was allowed to stand for two days, at the end of which time the white needle crystals were filtered off and washed thoroughly, first with alcohol and then with ether. The product so obtained dissolved readily in water to yield a clear, colorless solution. During the hydrolysis some of the substance reverted to benzalacetophenone, thus reducing somewhat the yield of the potassium salt. In general, the weight of the potassium salt which was obtained was greater than that of ester which was used: the best yield was 270 g. of potassium salt from 200 g. of ethyl ester.

The reduction of the ketonic acid yielded an acid reaction product which was very soluble in ether. The ether deposited crystals which were so soluble in ether that they could not be washed on the filter. The mother-liquors were viscous and difficult to handle. They finally set to a pasty mass of very small crystals, and this at length dried to a white, brittle, powdery mass. This white, brittle mass was worked up directly with acetic anhydride, for it was found that this part of the synthesis went smoothly and that good yields of the unsaturated acid were obtained.

Reduction of the δ-Ketonic Acid.—In one experiment 103 g. of the potassium salt was dissolved in a liter of water in a tall, glass cylinder and a large excess of sodium amalgam—21 g. of sodium in 900 g. of mercury—was thrown in. After 4 days, when the reaction appeared to be over, the solution was iced, made acid with hydrochloric acid, and shaken out with ether. The material deposited from the ether could not be manipulated and it finally yielded a crystal mush weighing 77 g. This was taken up in a hot mixture of benzene with a little methyl alcohol, and subjected to a systematic fractional crystallization. There was obtained 2 g. of a pure substance which was evidently—

β,δ-Diphenyl-δ-hydroxy-butyric Acid Lactone, 

$$C_6H_5\text{—}\underset{\llcorner\!\text{———O———————}}{CH}\text{—}CH_2\text{—}CH(C_6H_5)\text{—}\underset{C=O}{\overset{}{CH_2}}$$

.—It crystallizes from ethyl alcohol in beautiful, transparent, colorless needles, melting at 113–114° without decomposition. The crystals are not soluble in sodium carbonate solution either hot or cold. Their solution in alcohol gives a marked yellow color with one drop of ferric chloride solution—a much deeper color then results when one drop of ferric chloride is added to the same amount of pure alcohol. Half a gram of the substance boiled for half an hour with about 5 times its weight of acetic anhydride was recovered unchanged when the acetic anhydride was poured into water, the water shaken out with ether, and the ether allowed to evaporate. The substance dissolves in wet alcoholic potash and there is no precipitate when the alcoholic solution is diluted with a large quantity of water; but, if this solution is made acid and extracted with ether, the ether deposits the original substance. These are the properties of a lactone.

Calc. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.347. Found: C, 80.89; H, 6.518.

The properties of the substance and its composition indicate that it is the δ-lactone.

The conjunction of the two facts, that the substance was not altered by boiling with acetic anhydride, and that it did not appear in the product of any of the experiments in which the crude product of the reduction was boiled with acetic anhydride, indicates that it was probably formed, not as an intermediate product of the reduction, but because of the manner in which the reduction product was handled.

In another reduction experiment 270 g. of the potassium salt was treated, as before, with sodium amalgam consisting of 21 g. of sodium and 900 g. of mercury. After 4 days the aqueous solution was iced and acidified with hydrochloric acid. An oil separated. The sides of the container were scratched with a glass rod, and the next morning it was found that the oil has solidified to a mass of crystals. These, washed with water and dried, melted at 114–117° with decomposition. By fractional crystallization from benzene with a little methyl alcohol, and by extraction of the lower melting fractions with hot water, two substances were isolated—(*a*) the hydroxy-malonic acid derivative which constituted perhaps 3% of the reaction product, and (*b*) β,δ-diphenyl-δ-hydroxy-butyric acid which made up the large part of the reaction product.

2,4-Diphenyl, 4-Hydroxy-butane, Diacid-1,1 crystallizes from warm water, in which it is fairly soluble, in wart-like masses of colorless, radiating, stout needles which melt at 190–195° and turn brown and give off gas at the melting point. It is readily soluble in sodium carbonate solution from which it liberates gas.

Calc. for $C_{18}H_{18}O_5.2H_2O$: C, 61.72; H, 6.285. Calc. for $C_{18}H_{18}O_5.3H_2O$: C, 58.65 H, 6.570. Found: C, 60.64, 59.96; H, 5.572, 4.831.

The properties of the substances are in accord with the belief that it is a malonic acid derivative. It seems probable therefore that it is 2,4-diphenyl, 4-hydroxy-butane diacid-1,1 which had crystallized with two molecules of water and which had decomposed slightly, losing some carbon dioxide and some of its water.

β,δ-Diphenyl-δ-hydroxy-butyric Acid is but little soluble even in hot water. It dissolves readily in sodium carbonate solution. It crystallizes, with half a molecule of water of crystallization, in colorless needles from benzene and in pearly flakes from alcohol, and melts at 154–154.5° with the evolution of gas but without the production of any color.

Calc. for $2[C_{17}H_{18}O_3].H_2O$: C, 73.10; H, 6.861. Found: C, 73.08; H, 6.603.

The structure of this acid is demonstrated by its properties and composition, and by the fact that it yields the desired unsaturated acid when it is boiled with acetic anhydride.

Elimination of Water from the Reduced Acid.—Since it was found that the principal product of the reduction is a substance that yields the desired unsaturated acid when it is boiled with acetic anhydride, and since it was found that the unsaturated acid is much easier to isolate from its reaction mixture than the corresponding hydroxy-acid, it was found expedient to treat the crude product of the reduction at once with acetic anhydride without previous purification. The yields were fair. Two typical experiments are described.

18 g. of the white, brittle crude reduced acid was boiled for an hour with 50 cc. of acetic anhydride to which 8 drops of conc. sulfuric acid had been added. The mixture was poured into ice-water. An oil separated. After standing overnight, the oil had become a sticky solid. This was washed in water and dried in a vacuum desiccator—yielding 18.8 g. of a brown putty-like mass which smelled strongly of acetic acid. This was taken up in hot benzene and the solution yielded crystals from which, after several crystallizations, 9.6 g. of the pure unsaturated acid was obtained. The residue was a tar from which nothing further could be isolated.

82 g. of the crude reduced acid was boiled for an hour with 200 cc. of acetic anhydride to which about one cc. of conc. sulfuric acid had been added. The mixture was poured into water and allowed to stand for two days. The black, putty-like mass which resulted was recrystallized from benzene, yielding 23.6 g. of the pure unsaturated acid.

2,4-Diphenyl-butene-3 Acid-1 crystallizes from benzene in colorless, rhomb-shaped needles, m. p. 124–125°. It is somewhat soluble in hot water, from which it is deposited, when the solution cools, in transparent needles. It dissolves readily in aqueous sodium carbonate solution, and the solution discharges the color of permanganate instantly.

Calc. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.34. Found: C, 80.00, 80.96; H, 6.421, 6.404.

Molecular-weight determinations by measurement of the freezing points of benzene solutions gave the figures 537.9 and 439.0.

Calc. for $(C_{17}H_{16}O_2)_2$: 504.

It appears therefore that the acid exists in benzene solution in the form of a double molecule. The structure of the acid is demonstrated by the fact that it yields benzoic acid and phenyl-succinic acid on oxidation.

$$C_6H_5—CH = CH—CH(C_6H_5)—CH_2—COOH + 4[O] \longrightarrow$$
$$C_6H_5—COOH + C_6H_5—CH(COOH)—CH_2—COOH.$$

When a boiling aqueous solution of the sodium salt was oxidized with potassium permanganate, the odor of benzaldehyde appeared, and, later, the odor of benzoic acid. Nothing but benzoic acid could be isolated from the reaction product. When the oxidation was carried out in an iced solution, the manganese dioxide dissolved by the addition of sulfurous acid, the solution made acid and shaken out with ether, the ether deposited an oil which smelt strongly of benzaldehyde. After standing for a few weeks in the laboratory, the oil showed the presence of crystals; the odor of benzaldehyde had disappeared and an odor of aliphatic aldehydes remained. At the end of 8 weeks, the mass had crystallized in large part. By fractional crystallization and by extraction of the higher melting fraction with chloroform, the material was divided into benzoic acid and phenyl-succinic acid, which were identified by their melting points.

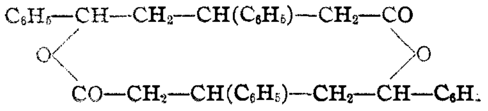
2,4-Diphenyl-butene-3 Acid-1 Methyl Ester.—The methyl ester first obtained by the action of methyl iodide in ether solution on the silver salt of the acid proved to be an oil, and the usual expedients—such as scratching with a glass rod, leaving in a vacuum desiccator, or freezing the methyl alcohol solution with liquid air—failed, to make it crystallize. A few drops, however, in the bottom of a beaker finally crystallized in white needles after a month's standing in the corner of the laboratory. With this *seed* at hand, the preparation of a larger amount was carried out successfully. The ester crystallizes from methyl alcohol in beautiful, radiating clusters of thick, transparent needles, m. p. 47-8°. In acetone solution it discharges the color of permanganate instantly.

Calc. for $C_{18}H_{18}O_2$: C, 81.21; H, 6.766. Found: C, 81.16; H, 7.423.

β,δ-Diphenyl-δ-hydroxy-butyric Acid Self Ester was obtained as a by-product in one preparation of the unsaturated acid, and in one only. The experiment in which this substance was obtained differed, so far as I know in no essential respect from similar experiments in which none of the substance appeared. 31 g. of the crude reduction product of the ketonic acid was boiled for half an hour with 100 g. of acetic anhydride to which 8 drops of conc. sulfuric acid had been added, the mixture was treated with water, and shaken out with ether. The ether deposited crystals which yielded, on recrystallization from benzene, 8 g. of a pure substance which crystallized from benzene in colorless, transparent needles, m. p. 92-94°. The substance is not soluble in sodium carbonate solution and, when warmed with a strong solution, it melts but does not dissolve. Its solution in acetone reduced permanganate rapidly but not instantly.

Calc. for $C_{34}H_{32}O_4$: C, 80.95; H, 6.347. Found: C, 81.17, 81.36; H, 6.066, 5.987.

The analysis is in good agreement with the belief that this substance is the "self ester" of β,δ-diphenyl, δ-hydroxy-butyric acid, formed from that acid by the combination of two molecules and the consequent elimination of two molecules of water.



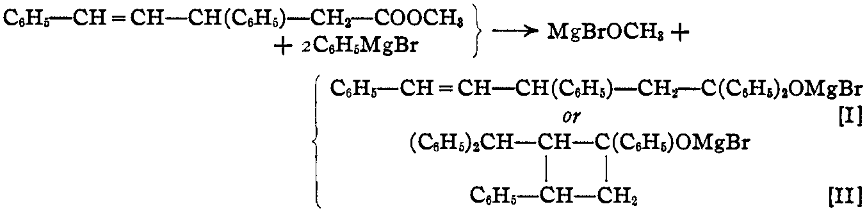
This hypothesis was verified by experiment. A quantity of the substance was dissolved in wet alcoholic potash and the solution was allowed to stand for 3 days. On diluting it with a large quantity of water, there was no precipitate. The solution was made acid and shaken out with ether. The ether deposited the expected acid in a state of purity.

Attempts to Reduce the Unsaturated Acid.—3 g. of 2,4-diphenylbutene-3 acid-1 was dissolved in aqueous sodium carbonate solution in a 50 cc. graduate, and sodium amalgam, consisting of one g. of sodium and 50 g. of mercury, was thrown in. After several days, when the evolution of gas had ceased, the solution was acidified and shaken out with ether. From the ether only the original acid and no other substance was obtained.

A repetition of the experiment gave the same result.

5 g. of the acid, 30 g. of zinc dust, 60 cc. of glacial acetic acid, and 5 cc. of water were boiled together under reflux for two hours. The mixture was treated with water and ether, and the ether proved to contain only the original acid and no other substance. The unsaturated acid, therefore, is not reduced under these conditions.

Reaction of the Methyl Ester with Phenyl Magnesium Bromide.—The methyl ester reacts in dry ether with two equivalents of phenyl-magnesium bromide. Immediately upon mixing the substances, there is a white precipitate, and indeed the entire appearance of the reaction is similar to that of the reaction of ethyl benzoate and phenyl-magnesium bromide. Two reactions are possible.



$$\left.\begin{array}{r} C_6H_5\text{—}CH=CH\text{—}CH(C_6H_5)\text{—}CH_2\text{—}COOCH_3 \\ +\ 2C_6H_5MgBr \end{array}\right\} \longrightarrow MgBrOCH_3 + \left\{\begin{array}{lr} C_6H_5\text{—}CH=CH\text{—}CH(C_6H_5)\text{—}CH_2\text{—}C(C_6H_5)_2OMgBr & \\ \qquad\qquad\qquad\qquad or & [I] \\ \qquad (C_6H_5)_2CH\text{—}\begin{array}{c}CH\\|\\C_6H_5\text{—}CH\end{array}\text{—}\begin{array}{c}C(C_6H_5)OMgBr\\|\\CH_2\end{array} & [II] \end{array}\right.$$

The product, which is obtained in a state of purity when the reaction mixture is treated with water, reduces permanganate in acetone solution indicating that the reaction is in accord with the first of the two equations above and that the γ,δ-unsaturated ester does not react in the 1,6-positions with the Grignard reagent under these conditions.

The product of the Grignard reaction consisted of only one substance, crystallizing from hot alcohol, in which it was not very soluble, in beautiful, colorless, thin needles, m. p. 138–139°. A solution of the substance in acetone discharges the color of permanganate instantly. It dissolves in conc. sulfuric acid to yield an orange-colored solution.

Calc. for $C_{29}H_{26}O$: C, 89.23; H, 6.667. Calc. for $C_{29}H_{25}OC_{29}H_{25}$: C, 91.36; H, 6.561. Found: C, 88.82, 89.45; H, 7.506, 7.05.

The analysis indicates that the substance which was isolated is the carbinol and not the corresponding ether. When a gram of the carbinol was boiled for half an hour with acetic anhydride and the reaction mixture was poured into alcohol, the original substance was recovered unchanged. It, therefore, does not form a stable acetate under these conditions. This fact, however, is quite in harmony with the conduct of other tertiary alcohols of this type.

SOMERVILLE, MASS.

[CONTRIBUTION FROM THE CARBOHYDRATE LABORATORY, BUREAU OF CHEMISTRY, UNITED STATES DEPARTMENT OF AGRICULTURE.]

THE AMIDE OF α-*d*-MANNOHEPTONIC ACID.

BY C. S. HUDSON AND K. P. MONROE.

Received May 15, 1919.

This substance was first noted by Fischer[1] as a precipitate settling from the reaction mixture of hydrogen cyanide and *d*-mannose in aqueous solution. He identified the substance as an amide by its behavior towards alkalies and iron salts, found its m. p. to be 182–3°, but published no analysis or record of its purification. Its specific rotation was not measured. As we desired to know its rotatory power we prepared it in similar manner but soon reached the conclusion that it was by no means a pure compound because on successive recrystallizations its m. p. rose to 193–4° and its specific rotation increased from +4 to +28°. These higher values were found only after the substance had been recrystallized 6 times but further recrystallization did not change them. As the substance was difficult to purify and there seeemed a possibility of the presence in it of the isomeric β-*d*-mannoheptonic amide, or some other impurity, a second method for preparing it was studied. Ten g. of pure crystalline α-*d*-mannoheptonic lactone was dissolved in 100 cc. of 50% alcohol, the solution was cooled with ice and ammonia was passed into it to saturation. A fine, white, granular precipitate formed, which was filtered off and washed with cold 50% alcohol. Its m. p. was 184–5° and $[\alpha]_D^{20} = +14$. After only two recrystallizations from hot water its m. p. was 193–4° and $[\alpha]_D^{20} = +27.8°$, both of which agree with the values found for the other preparation of this amide.

The purified amide from the hydrogen cyanide reaction was found to contain 6.1% and 5.9% N in two analyses by the Kjeldahl method, which agree with the theoretical value for $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHOH.CONH_2$, 6.2%. The purified amide made by the action f ammonia on the lactone gave 5.9% and 6.1% N. An aqueous solution of the purified amide from the HCN reaction, containing 0.542 g. substance in 50 cc. solution rotated 1.21° to the right at 20° in a 4 dcm. tube

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[1] *Untersuchungen über Kohlenhydrate und Fermente*, p. 300.