α-acetamino-β-aminopropionic acid and of the corresponding α,β-diamino acid.

Accordingly, acetyldehydroalanine was refluxed in ethanolic solution with benzylamine. From the reaction mixture three products were isolated in crystalline form. In the order of their isolation there was obtained alanine (16%), α-amino-β-benzylaminopropionic acid (15%) and α-acetamino-β-benzylaminopropionic acid (25%), the figures in parentheses relating to the yields based on the acetyldehydroalanine employed. When absolute methanol was used instead of ethanol in the saturation reaction, no alanine was isolated, and the yields of α-amino-β-benzylaminopropionic acid and of α-acetylamino-β-benzylaminopropionic acid were, respectively, 20 and 32%. Catalytic reduction of α-acetamino-β-benzylaminopropionic acid led to α-acetamino-β-aminopropionic acid which on HCl hydrolysis gave α,β-diaminopropionic acid·HCl in good yield.

The formation of α-amino-β-benzylaminopropionic acid in the saturation reaction was no doubt due to the splitting off of the acetyl group from the addition product. The formation of alanine in this reaction, and to so appreciable an extent, is more difficult to explain, but it is not inconceivable that under the conditions used the amino acid might owe its origin to a reductive reaction among the degradation products of acetyldehydroalanine which would include ammonia and pyruvic acid. The lower refluxing temperature in the presence of methanol than of ethanol might be insufficient to permit this reaction to proceed.

Experimental

Reaction of Acetyldehydroalanine with Benzylamine.—Ten grams of acetyldehydroalanine[6] was suspended in a solution of 100 ml. of freshly distilled benzylamine in 50 ml. of absolute ethanol, and the reaction mixture refluxed for six hours in the absence of atmospheric carbon dioxide. After cooling the solution to 25°, 500 ml. of acetone was added and the mixture chilled at −10° for several hours. The precipitate (1.1 g.) which appeared was filtered off and recrystallized from water by addition of excess acetone. Paper chromatograms in several solvents, together with an infrared spectrogram revealed that the material was alanine, evidence which was confirmed further by the analytical data.

Anal. Calcd. for $C_3H_7O_2N$: C, 40.5; H, 7.9; N, 15.7. Found: C, 40.7; H, 7.8; N, 15.6.

The filtrate from the above precipitate was evaporated *in vacuo* nearly to dryness and 200 ml. of acetone again added. A slightly yellowish crystalline material separated (2.2 g.). The crude product was dissolved in water, the solution clarified with Norit, and after filtration a large volume of absolute ethanol added to the filtrate. The colorless precipitate which appeared was purified again in the same way. Analysis revealed nearly pure α-amino-β-benzylaminopropionic acid.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.8; H, 7.2; N, 14.5. Found: C, 61.6; H, 6.9; N, 14.3.

The filtrate from the above isolation which was a light brown viscous liquid was treated with 200 ml. of 2 *N* NaOH and extracted four times with ethyl ether. Dilute HCl was added to the aqueous layer until the reaction was slightly acid to congo red, the solution was evaporated *in vacuo* to dryness, and the residue extracted three times with absolute ethanol. The combined ethanolic extracts were evaporated *in vacuo* to dryness, and chloride ion removed by addition of a suspension of silver carbonate in water. Silver ion subsequently was removed with H_2S gas and the final filtrate evaporated *in vacuo* to a low bulk. Appearance of crystals at this stage was further facilitated by addition of excess ethanol. The crude yield of α-acetamino-β-benzylaminopropionic acid was 4.5 g. The compound was recrystallized from hot 85% ethanol, and melted at 188°.

Anal. Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.0; H, 6.8; N, 11.9. Found: C, 60.7; H, 6.7; N, 11.9.

Repetition of the above procedure, using methanol instead of ethanol in the saturation reaction of benzylamine with acetyldehydroalanine yielded no alanine but only α-amino-β-benzylaminopropionic acid and α-acetamino-β-benzylaminopropionic acid in yields of 20 and 32%, respectively.

Treatment of α-amino-β-benzylaminopropionic acid with a hot mixture of acetic anhydride in glacial acetic acid yielded the α-acetamino compound which was isolated after pouring the reaction mixture into cold water. After recrystallization from 85% ethanol, the compound melted at 188°. The yield was 60%.

Anal. Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.0; H, 6.8; N, 11.9. Found: C, 61.1; H, 6.9; N, 11.5.

Preparation of α,β-Diaminopropionic Acid.—Three grams of α-acetamino-β-benzylaminopropionic acid, isolated as above from the reaction mixture of benzylamine and acetyldehydroalanine, was dissolved in 75 ml. of 50% methanol, the solution treated with a few drops of acetic acid, and subjected to catalytic hydrogenation at 40 lb. in the presence of palladium. The reaction was ended in two and a half hours, and after removal of the catalyst the solution was evaporated *in vacuo* to a volume of about 10 ml. Addition of acetone caused the separation of a colorless oil which crystallized on chilling to −10°. The compound, α-acetamino-β-aminopropionic acid, sintered at 181° and decomposed at 197°. The yield was 1.2 g.

Anal. Calcd. for $C_5H_{10}O_3N_2$: C, 41.1; H, 6.9; N, 19.1. Found: C, 41.0; H, 7.1; N, 18.8.

When the α-acetamino-β-aminopropionic acid was refluxed with 2 *N* HCl for two hours the acetyl group was hydrolyzed off, and α,β-diaminopropionic acid monohydrochloride isolated by addition of excess ethanol to the condensed reflux mixture. The yield was about 80%.

Anal. Calcd. for $C_3H_9O_2N_2Cl$: C, 25.6; H, 6.5; N, 19.9; Cl, 25.2. Found: C, 25.5; H, 6.6; N, 19.5; Cl, 25.0.

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(6) M. Bergmann and K. Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

Reactions of the Bromomagnesium Salt of N,N-Dimethyl-β,β-diphenylpropionamide

BY GERALD GILBERT[1]

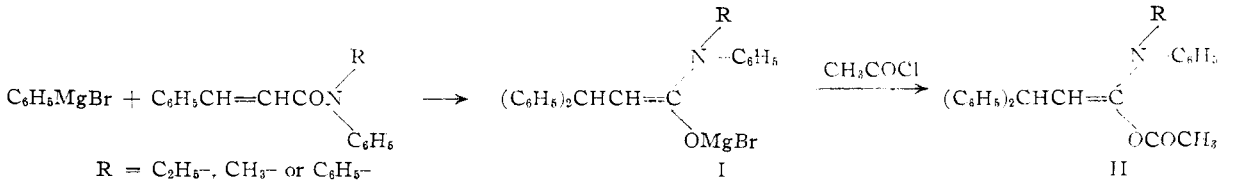
RECEIVED MARCH 18, 1955

The conjugate addition of Grignard reagents to α,β-unsaturated amides has been reported to yield the intermediates I.[2] Maxim and Ioanid claimed that the acylation of these substances formed the enol esters II and that this evidence established the addition as proceeding by a 1,4-mechanism.[3] The structure of the acylated derivatives was proved by hydrolysis with alcoholic potassium hydroxide. Where R was methyl or ethyl, the corresponding anilide of β,β-diphenylpropionic acid was isolated. Where R was phenyl, hydrolysis yielded β,β-diphenylpropionic acid itself.

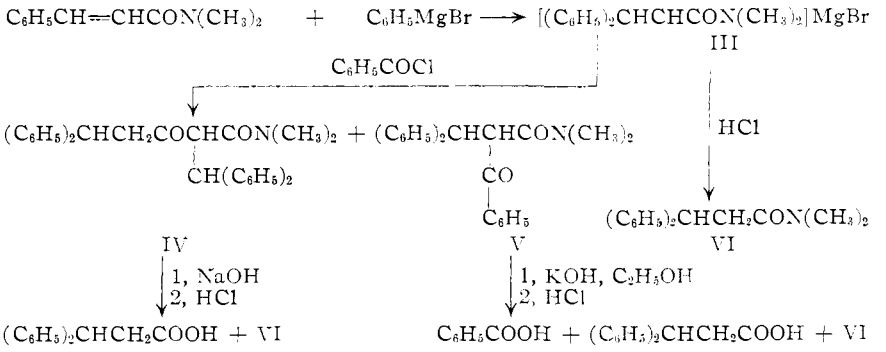
(1) Medicinal Chemistry Branch, Chemical Corps Medical Laboratories, Army Chemical Center, Md.

(2) N. Maxim and N. Ioanid, *Bull. soc. chim. Romania*, **10**, 116 (1928).

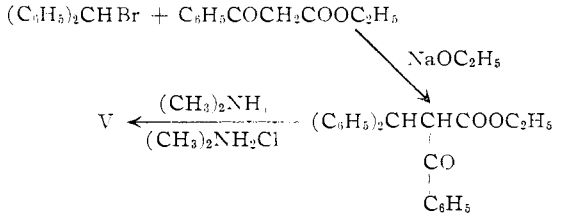
(3) The evidence, however, does not in itself favor any mechanism for the conjugate addition of the Grignard reagent since, for example, it has been shown that the acylation of intermediates formed by addition to unsaturated ketones yields products which vary with the structure of the ketone. See E. P. Kohler, M. Tishler and H. Potter, THIS JOURNAL, **57**, 2517 (1935).



In the present work, an enol ester similar to II was desired as a synthetic intermediate. Phenylmagnesium bromide was condensed with N,N-dimethylcinnamamide and the magnesium salt III treated with benzoyl chloride, yielding two principal products. The ether-insoluble substance, m.p. 211.6–212.2°, crystallized unchanged from ethanol and gave a slight red color with ferric chloride. Saponification with alcoholic potassium hydroxide for four hours yielded β,β-diphenylpropionic acid, benzoic acid and N,N-dimethyl-β,β-diphenylpropionamide (VI), all identified by mixed melting points with authentic samples. Although this evidence and the data presented by Maxim and Ioanid are consistent with the enol ester structures, they do not distinguish between these and the C-acyl derivatives, in the present case the β-keto amide V. Since the other evidence was not sufficient to differentiate between the two, synthetic evidence was sought by an unequivocal preparation of V, which the properties of the substance indicated to be the most likely and most easily accessible of the two possibilities.

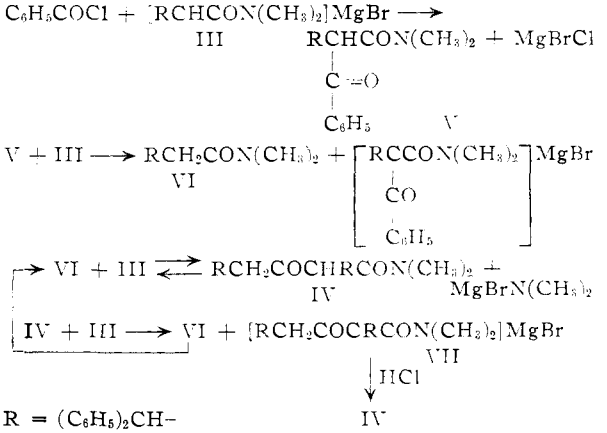


Ethyl α-benzhydrylbenzoylacetate was prepared according to the method of Kohler and Tishler.[4] Uncatalyzed aminolyses with dimethylamine at room temperature and 160° were unsuccessful. However sufficient conditions for the transformation were obtained by passing gaseous dimethylamine through the molten ester in the presence of dimethylamine hydrochloride at 190–205°. The identity of the compound thus obtained and that formed by benzoylation of III was established by a melting point and a mixed melting point. The close resemblance of the starting amides indicates that the acylated substances obtained by Maxim and Ioanid are probably also β-keto amides.



The ether-soluble compound obtained by acylation of III was a white solid, m.p. 194.8–195.5°, which yielded VI and β,β-diphenylpropionic acid on saponification. These data and the elemental analyses indicate the substance to be N,N-dimethyl-α,γ-dibenzhydrylacetoacetamide (IV), another β-keto amide which is apparently produced by the self condensation of III. The existence of the latter in the reaction mixture in high yield was established by hydrolysis with dilute acid, yielding 93% of VI, the expected saturated amide.

A possible mechanism for the formation of IV is outlined below. The acylation of the magnesium salt III yields V which contains a β-keto amide group and, being more acidic, exchanges with III to form the saturated amide VI. This can undergo condensation with III to yield IV by a route similar to that usually postulated for the acetoacetic ester condensation. IV also can undergo exchange with III to yield VI and continue the reaction. Hydrolysis of the magnesium salt VII yields IV, the product isolated.



The yields of the two main products varied considerably in several similar runs. In one experi-

(4) E. P. Kohler and M. Tishler, THIS JOURNAL, **54**, 1599 (1932).

ment, 10% of IV and 45% of V were obtained, while in a second run 61% of the former and none of the latter was isolated. Although the factors involved were not investigated further, an examination of the mechanism indicates that small variations in experimental conditions might account for large fluctuations in the yields. For example, the rate of addition of the benzoyl chloride may control the formation of V and of VI, which acts essentially as a catalyst for the condensation. Acylation of the dimethylamide ion formed in the reversible condensation step also may influence the relative rates of formation of V and VII.

Experimental

Benzoylation of III.—A saturated ethereal solution of 2.33 g. (0.0133 mole) of N,N-dimethylcinnamamide, prepared by the method of Staudinger and Kon,[5] was added to a solution of phenylmagnesium bromide (from 3.55 g. (0.023 mole) of bromobenzene) and stirring continued for one-half hour. The addition of the amide was carried out slowly enough to avoid the precipitate which is characteristic of the formation of complex products and was ended when the precipitate persisted.[6]

The mixture was cooled in an ice-bath and 2.82 g. (0.02 mole) of freshly distilled benzoyl chloride in 50 ml. of ether added slowly with stirring. The mixture was hydrolyzed with 70 ml. of cold 8% hydrochloric acid and stirred for one-half hour. On filtration, 2.13 g. (45%) of N,N-dimethyl-α-benzoyl-β,β-diphenylpropionamide, m.p. 211.6–212.2° from 95% ethanol, was obtained.

Anal. Calcd. for $C_{24}H_{23}O_2N$: C, 80.64; H, 6.49. Found: C, 80.90; H, 6.51.

Evaporation of the dried ether extract of the hydrolysate after filtration yielded 0.3 g. (10%) of N,N-dimethyl-α,γ-dibenzhydrylacetoacetamide, identified by a mixed melting point with the sample obtained below.

In a second run, a 1.7-mole excess of benzoyl chloride over the amide was used and the addition carried out more rapidly. Under these conditions, no IV was isolated but a 61% yield of V was obtained, m.p. 194.8–195.4°.

Anal. Calcd. for $C_{32}H_{31}O_2N$: C, 83.23; H, 6.72; N, 3.04. Found: C, 83.36; H, 6.56; N, 3.24.

Hydrolysis of III.—Phenylmagnesium bromide from 5 g. (0.032 mole) of bromobenzene was treated with an ethereal solution of 2.45 g. (0.014 mole) of N,N-dimethylcinnamamide. Stirring was continued for one-half hour longer. The solution was hydrolyzed with 70 ml. of 8% hydrochloric acid and the ether solution separated and dried. On evaporation of the solvent, 4 g. of a yellow solid was obtained which contained 3.33 g. (93%) of N,N-dimethyl-β,β-diphenylpropionamide, m.p. 114–114.2°, recrystallized from 60–68° petroleum ether. The substance did not depress the melting point of an authentic sample prepared from β,β-diphenylpropionyl chloride and dimethylamine.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.60; H, 7.57. Found: C, 80.83; H, 7.24.

Hydrolysis of IV.—A solution of 0.13 g. of IV, 25 ml. of 95% ethanol and 4 g. of potassium hydroxide was maintained at reflux for four hours. The solvent was removed under reduced pressure, the residue dissolved in 25 ml. of water, extracted with ether to remove neutral material and the ether extract dried over anhydrous sodium sulfate. Removal of the solvent yielded 0.033 g. of N,N-dimethyl-β,β-diphenylpropionamide, m.p. 111–112°. A mixed melting point with an authentic sample showed no depression.

The water solution of the potassium salts was made acidic with cold concentrated hydrochloric acid and extracted with ether. On removal of the solvent, a mixture of two acids was obtained which was separated by sublimation under reduced pressure on a steam-bath. The sublimate crystallized from water in long needles, m.p. 119–121°. A mixed melting point with an authentic sample of benzoic acid showed no depression. The sublimation residue was recrystallized from 60–68° petroleum ether, m.p. 155–156°. A mixed melting point with an authentic sample of β,β-diphenylpropionic acid showed no depression.

Hydrolysis of V.—This compound (0.38 g.) was refluxed for four hours with 20 ml. of 95% ethanol and 20 ml. of 10% sodium hydroxide solution. The solvent was removed under reduced pressure, and the residue taken up in water and extracted with ether. The ethereal solution was dried, the solvent removed and the residue recrystallized from 60–68° petroleum ether; m.p. 111–112°. A mixed melting point with an authentic sample of N,N-dimethyl-β,β-diphenylpropionamide showed no depression.

The aqueous solution was acidified precipitating a white solid which was recrystallized from alcohol–water solution; m.p. 154.5–156°. A mixed melting point with an authentic sample of β,β-diphenylpropionic acid showed no depression.

IV.—One gram (0.0029 mole) of ethyl α-benzhydrylbenzoylacetate prepared by the method of Kohler and Tishler[4] was mixed with 0.2 g. (0.003 mole) of dry dimethylamine hydrochloride and placed in a small test-tube. The mixture was melted and kept at 190–205° while a brisk stream of dimethylamine was passed in. After one-half hour the melt solidified and the product was cooled and recrystallized from an alcohol–water solution; m.p. 209–211°, yield 0.4 g. (39%). A mixed melting point with IV obtained above showed no depression.

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(5) H. Staudinger and N. Kon, *Ann.*, **384**, 119 (1911).

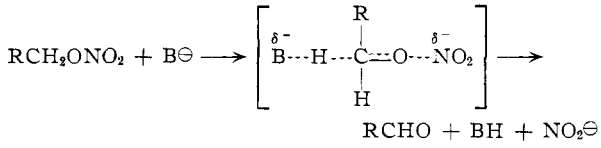
(6) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 21 (1905).

The Synthesis of Diketones from Nitratoketones[1]

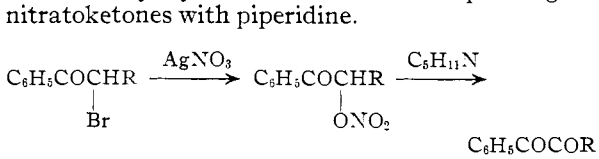
BY WILLIAM D. EMMONS AND JEREMIAH P. FREEMAN

RECEIVED MARCH 21, 1955

Previously it had been shown that trichloroethyl nitrate is degraded to chloral in almost quantitative yields when treated with secondary amines.[2] This reaction is an example of the α-elimination reaction[3] of nitrate esters which involves abstraction of an α-hydrogen atom by the base and elimination of nitrite ion, the process probably being concerted.



The rapid rate at which this reaction proceeded and the high yields obtained from it suggested that it might be a useful synthetic route to negatively substituted ketones and aldehydes. Indeed it has been found that aryl α-diketones may be prepared conveniently by reaction of the corresponding α-nitratoketones with piperidine.



The nitratoketones were synthesized readily from the α-bromo compounds by means of silver nitrate in acetonitrile.[4] The over-all yields both of nitratoketones and diketones are summarized in Table I.

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-234.

(2) W. D. Emmons, K. S. McCallum and J. P. Freeman, *J. Org. Chem.*, **19**, 1472 (1954).

(3) J. W. Baker and D. M. Easty, *J. Chem. Soc.*, 1207 (1952).

(4) A. F. Ferris, K. W. McLean, I. G. Marks and W. D. Emmons, THIS JOURNAL, **75**, 4078 (1953).