VI.— β -Amino- β -phenylpropiophenone.

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α -AMINO-KETONES, for example, α -aminopropiophenone, exhibit great instability in the free state on account of their tendency to condense in the presence of air to give substituted pyrazines (Gabriel, *Ber.*, 1908, **41**, 1127). On the other hand, β -amino-ketones are much more stable; diacetoneamine is exceptional, as it can even be distilled, but other ketones of this class are not nearly so stable; thus Gabriel (*Ber.*, 1908, **41**, 242) has shown that β -aminopropiophenone evolves ammonia when heated with aqueous potassium hydroxide, and it does not appear from his description that the compound is stable enough to be kept at the ordinary temperature for any length of time.

For the purpose of another research it was desired to obtain a β -amino-ketone containing an asymmetric carbon atom, and the preparation of β -amino- β -phenylpropiophenone was accordingly undertaken by the authors in the hope that this compound would be sufficiently stable to permit of its isolation. The preparation was carried out as follows. Cinnamic acid was converted into β -amino- β -phenylpropionic acid, from which the corresponding *phthalimino-acid* was obtained by heating with phthalic anhydride. The action of benzene and aluminium chloride on the chloride of the *phthalimino-acid* led to β -*phthalimino- β -phenylpropiophenone*, which was converted by means of aqueous alkali into the corresponding *phthalamic acid* (compare Gabriel, *Ber.*, 1908, **41**, 242, 513, and other papers by the same author). The hydrolysis of the *phthalamic acid* was accomplished by a mixture of glacial acetic acid and concentrated hydrochloric acid. The resulting hydrochloride on decomposition with ammonia gave β -amino- β -phenylpropiophenone as a solid melting at 82—83°. The free amino-ketone is much more stable at the ordinary temperature than is desylamine, the related α -amino-ketone.

An attempt was made to obtain the ketone by a more direct method, namely, by the action of magnesium phenyl bromide on β -amino- β -phenylpropionanilide, $\text{NH}_2\cdot\text{CHPh}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NHPh}$. The disruption of the additive compound by aqueous ammonium chloride led, however, to the regeneration of the anilide. The result would suggest that the additive compound may have been

in which case the rearrangement into a product giving the amino-ketone on hydrolysis did not occur. Now it has been found by McKenzie, Martin, and Rule (T., 1914, **105**, 1583) that the action of Grignard reagents on alkylated acid amides (for example, *r*-mandeloethylamide and *l*- β -hydroxy- β -phenylpropionethylamide) does not always lead to the formation of the corresponding ketols, and it seems probable that the additive compounds formed in those cases may also have been of the oxonium type postulated above.

v. Braun has, in fact, suggested the structure
$$\begin{array}{c} \text{R}_2\text{N} \\ | \\ \text{R} > \text{C} : \text{O} < \text{MgHlg} \\ | \\ \text{R}' \end{array}$$

for the compounds obtained from dialkylated amides. The recent work of v. Braun, Heider and Müller (*Ber.*, 1917, **50**, 1637) and of v. Braun and Kirschbaum (*Ber.*, 1919, [B], **52**, 1725) on the action of Grignard reagents (prepared from bromoalkylated anilines) on aldehydes and ketones respectively certainly lends support to the view that the first phase in the addition of a Grignard reagent to an aldehyde or a ketone consists in the formation of an oxonium compound where the reagent attaches itself to the oxygen atom of the carbonyl group of the aldehyde or ketone. Such an additive compound would be labile enough to undergo, as a general rule, isomeric change with readiness prior to its hydrolysis, but apparently it may sometimes happen that this rearrangement does not occur.

The action of aluminium chloride on a solution of β -formylamino- β -phenylpropionyl chloride in benzene took an unexpected course, the product being $\beta\beta$ -diphenylpropiophenone. Now it is shown in the present paper that β -phthalimino- β -phenylpropionic acid decomposes on heating into carbon dioxide, phthalimide, cinnamic acid, and styrene, the last-named substance being doubtless formed from the cinnamic acid (I). This result suggested a similar course for

the decomposition of β -formylamino- β -phenylpropionyl chloride into formamide and cinnamoyl chloride (II), aluminium chloride acting as a catalyst. The cinnamoyl chloride formed in this manner then reacts with benzene and aluminium chloride with the formation of $\beta\beta$ -diphenylpropiophenone. The interaction of cinnamoyl chloride, benzene, and aluminium chloride, under the conditions described in

the experimental part, gave a mixture of $\beta\beta$ -diphenylpropionophenone and $\beta\beta$ -diphenylpropionic acid.

β -Benzoylamino- β -phenylpropionyl chloride differed from the formyl compound inasmuch as it underwent the normal reaction with benzene and aluminium chloride, the product being β -benzoylamino- β -phenylpropionophenone.

Some optically active derivatives of β -amino- β -phenylpropionic acid are at present under investigation by one of us (A. McK.).

EXPERIMENTAL.

β -Amino- β -phenylpropionanilide.

β -Amino- β -phenylpropionic acid was prepared by the action of hydroxylamine on cinnamic acid according to Posner's method (*Ber.*, 1905, **38**, 2316). Four grams of the well-dried and finely-powdered amino-acid were suspended in 20 c.c. of freshly-distilled acetyl chloride, the mixture was cooled in ice, and treated gradually with 5.3 grams of finely-powdered phosphorus pentachloride. The mixture was shaken during the addition of the pentachloride (fifteen minutes), and the shaking was continued for half an hour longer at the ordinary temperature. The resulting solid, β -amino- β -phenylpropionyl chloride hydrochloride, was separated and washed with acetyl chloride and light petroleum. A solution of 2.5 grams of it were suspended in dry ether, and treated at the ordinary temperature with a solution of 4.2 grams of aniline in ether. Water was then added, the aqueous solution separated, and made alkaline with sodium hydroxide. The anilide precipitated was crystallised from aqueous alcohol (Found, C=74.8; H=6.9. $C_{15}H_{16}ON_2$ requires C=75.0; H=6.7 per cent.).

β -Amino- β -phenylpropionanilide, $NH_2 \cdot CHPh \cdot CH_2 \cdot CO \cdot NHPh$, separates from ethyl alcohol in colourless plates melting at 122°. It is readily soluble in ethyl alcohol or chloroform, moderately so in benzene or ether, and sparingly so in light petroleum.

Attempts to prepare the amide and the piperidide of β -amino- β -phenylpropionic acid by the action of dry ammonia and of piperidine on a suspension of the chloride hydrochloride in dry ethereal solution gave amorphous products, probably due to polypeptide formation.

The anilide (1 mol.) was subjected to the action of magnesium phenyl bromide (6 mols.). On decomposing the additive compound with ammonium chloride the anilide was regenerated.

Action of β -Formylamino- β -phenylpropionyl Chloride on Benzene in the Presence of Aluminium Chloride.

The formylation of the amino-acid was carried out as described by Fischer, Scheibler, and Groh (*Ber.*, 1910, **43**, 2020), and the formyl acid then converted into its chloride by means of acetyl chloride and phosphorus pentachloride. The chloride, prepared from 3.9 grams of the formyl acid, was a viscid, yellow oil; it was dissolved in 50 c.c. of benzene, and acted on by 5 grams of aluminium chloride by heating on the water-bath for one hour. After decomposition with hydrochloric acid and removal of the benzene, the product was crystallised twice from ethyl alcohol, when lustrous needles (0.7 gram) separated. These melted at 94–95°, contained no nitrogen, and consisted of $\beta\beta$ -diphenylpropiophenone, $\text{CHPh}_2 \cdot \text{CH}_2 \cdot \text{COPh}$ (Found, C=88.1; H=6.5. Calc., C=88.1; H=6.3 per cent.). Kohler (*Amer. Chem. J.*, 1903, **29**, 352) gives m. p. 96°.

Action of Cinnamoyl Chloride on Benzene in the Presence of Aluminium Chloride.

This action had already been investigated by Kohler, Heritage, and Burnley (*Amer. Chem. J.*, 1910, **44**, 60) under somewhat different conditions to those employed by us. They found that $\beta\beta$ -diphenylpropiophenone was accompanied by 3-keto-1-phenyl-2:3-dihydroindene and β -chloro- β -phenylpropiophenone. The product obtained under the following conditions appeared to consist entirely of $\beta\beta$ -diphenylpropionic acid and $\beta\beta$ -diphenylpropiophenone.

A mixture of 10 grams of cinnamic acid and 14.8 grams of phosphorus pentachloride was heated on the water-bath for half an hour, the oxychloride removed under diminished pressure, and the resulting oil acted on by 50 c.c. of benzene and 10 grams of aluminium chloride. The action was completed by heating, and the mixture allowed to remain overnight. Dilute hydrochloric acid was added, the product extracted with ether, and the ethereal solution then shaken with sodium carbonate. On acidifying the alkaline extract with hydrochloric acid, 5.1 grams of $\beta\beta$ -diphenylpropionic acid were precipitated, which after crystallisation from ethyl alcohol separated in lustrous, white needles melting at 149–150°. Liebermann and Hartmann (*Ber.*, 1892, **25**, 2124), who obtained the acid as one of the products of the action of sulphuric acid on cinnamic acid and benzene, give m. p. 149°. (Equivalent=229.1. Calc.=226.)

After being dried with sodium sulphate, the ethereal solution on evaporation gave a red oil which solidified almost completely when

kept in the ice-chest for two days. The solid was freed from a small quantity of oil and purified by crystallisation from alcohol. It amounted to 11.5 grams, and consisted of $\beta\beta$ -diphenylpropio-phenone.

β -Benzoylamino- β -phenylpropio-phenone.

β -Amino- β -phenylpropionic acid was converted into its benzoyl derivative, which melted at 194—195°, whereas Posner (*loc. cit.*) gives 194—196°. Ten grams of the benzoylamino-acid were converted by means of acetyl chloride and phosphorus pentachloride into β -benzoylamino- β -phenylpropionyl chloride, which crystallises in needles. The latter was dissolved in 50 c.c. of benzene, and acted on by 10 grams of aluminium chloride. After the usual manipulation, 4.1 grams of a solid were isolated.

β -Benzoylamino- β -phenylpropio-phenone,

separates from ethyl alcohol in lustrous, slender, colourless needles melting at 152—154° (Found, C=79.9; H=6.1; N=4.3. $\text{C}_{22}\text{H}_{19}\text{O}_2\text{N}$ requires C=80.2; H=5.8; N=4.3 per cent.).

β -Phthalimino- β -phenylpropionic Acid.

A mixture of 11 grams of β -amino- β -phenylpropionic acid and 10.5 grams of phthalic anhydride were heated for two hours at 155—165°, at the end of which time the phthalimino-acid commenced to crystallise from the molten mass. On cooling, the acid was dissolved in 20 c.c. of hot glacial acetic acid, and 20 c.c. of benzene were added. On cooling, 13 grams of the crude acid separated. Purification was effected by crystallisation from benzene.

β -Phthalimino- β -phenylpropionic acid,

melts at 169.5—170.5°, is very readily soluble in hot ethyl alcohol or hot glacial acetic acid, moderately so in benzene, and very sparingly soluble in hot water. It separated from alcohol in slender needles (Found, C=69.1; H=4.7. $\text{C}_{17}\text{H}_{13}\text{O}_4\text{N}$ requires C=69.1; H=4.4 per cent.).

In a second preparation 35 grams of phthalic anhydride and 36 grams of the amino-acid gave 48 grams of the phthalimino-acid melting at 168—170° after one crystallisation from a mixture of 60 c.c. of glacial acetic acid and 60 c.c. of benzene.

The *acid chloride*, prepared by heating the acid with an excess of thionyl chloride for half an hour, separates from benzene in needles melting at 96—97°. For analysis it was dried over phos-

phoric oxide and paraffin wax (Found, Cl=10.6. $C_{17}H_{12}O_3NCl$ requires 11.3 per cent.).

The *anilide*, prepared by the interaction at the ordinary temperature of aniline and the acid chloride in ethereal solution, separates from glacial acetic acid in glistening prisms or rhomboidal plates melting at 238° . It is sparingly soluble in ethyl alcohol (Found, N=7.5. $C_{23}H_{18}O_3N_2$ requires N=7.6 per cent.).

The *methyl* ester, prepared by the esterification of the acid with methyl alcohol and hydrogen chloride, separates from ethyl alcohol in plates melting at 92° (Found, N=4.9. $C_{18}H_{15}O_4N$ requires N=4.5 per cent.).

The action of heat on β -phthalimino- β -phenylpropionic acid was studied. Evolution of carbon dioxide began at 240° and became vigorous at 300° . The temperature was maintained at 320 – 350° for half an hour. The liquid, which had a pronounced odour of styrene, was then distilled under ordinary pressure. The residue was dissolved in ethyl alcohol and decolorised with charcoal; phthalimide was isolated from it. The distillate solidified to a white, crystalline mass, which was crystallised twice from a mixture of ethyl alcohol and benzene; the product was identified as phthalimide. The alcohol-benzene solution from which the phthalimide had been separated was extracted with aqueous sodium carbonate, and cinnamic acid was obtained from the alkaline solution by acidification and extraction with ether.

β -Phthalimino- β -phenylpropiophenone.

The best conditions for the preparation of this compound were the following. Twenty-five grams of the phthalimino-acid were heated for half an hour on the water-bath with 20 grams of thionyl chloride until the evolution of hydrogen chloride ceased. The excess of thionyl chloride was removed by distillation under diminished pressure, when the acid chloride remained as a very viscid, yellow oil. Benzene (100 c.c.) was added to the warm oil, the greater part of which dissolved and, on cooling, separated in a mass of needles. Aluminium chloride (20 grams) was then added. Action soon started with evolution of hydrogen chloride. After remaining at the ordinary temperature overnight, the mixture was heated for twenty minutes, when a further vigorous evolution of hydrogen chloride took place. On cooling, water and hydrochloric acid were added, and the benzene removed by distillation in a current of steam. The ketone was left as a viscid, pale yellow oil, which solidified readily. It was separated and crystallised from ethyl alcohol. Yield, 26 grams.

β -Phthalimino- β -phenylpropiophenone,

separates from ethyl alcohol in needles melting at 116—117°. It is readily soluble in hot alcohol, but only moderately so in the cold solvent. It crystallises sluggishly, and tends to separate from hot concentrated solutions as an oil.

 β -Benzoyl- α -phenylethylphthalamic Acid.

β -Phthalimino- β -phenylpropiophenone (7.5 grams) was suspended in 20 c.c. of ethyl alcohol, and heated on the water bath for ten minutes with 30 c.c. of *N*-sodium hydroxide. The solution was diluted with 200 c.c. of water and acidified with hydrochloric acid. The phthalamic acid was precipitated as an oil, which on stirring coagulated to form a pasty mass, and this on remaining overnight became quite solid and friable. It was purified by crystallisation from ethyl alcohol.

 β -Benzoyl- α -phenylethylphthalamic acid,

separates from ethyl alcohol in needles melting at 132° (Found, $N=3.7$. $\text{C}_{23}\text{H}_{19}\text{O}_4\text{N}$ requires 3.8 per cent.). It is readily soluble in acetone, ethyl alcohol, or glacial acetic acid, moderately so in benzene, and sparingly soluble in light petroleum.

 β -Amino- β -phenylpropiophenone.

A solution of 10 grams of β -benzoyl- α -phenylethylphthalamic acid in 50 c.c. of hot glacial acetic acid was heated on the water-bath for one hour with 30 c.c. of concentrated hydrochloric acid; a small amount of a pale yellow oil separated on heating. On the addition of 150 c.c. of water a further quantity of oil was precipitated, which became pasty on shaking. The clear solution was separated and evaporated to about 50 c.c. under diminished pressure, separated from a further small quantity of oil, and finally evaporated to dryness under diminished pressure. The amino-ketone hydrochloride was obtained in this way in slender, colourless needles accompanied by a small amount of a viscid, yellow oil. The aqueous solution was extracted with ether and rendered alkaline with ammonia. The precipitated amino-ketone was extracted with ether, the ethereal solution dried with sodium sulphate, and the ether removed. The residual pale yellow oil solidified on cooling and was crystallised from a mixture of benzene and light petroleum. The yield was 0.75 gram.

β -Amino- β -phenylpropiophenone, $\text{NH}_2\cdot\text{CHPh}\cdot\text{CH}_2\cdot\text{COPh}$, crys-

tallises in soft, colourless leaflets melting at 82–83° (Found, $N=6.3$. $C_{15}H_{15}ON$ requires $N=6.2$ per cent.). It is readily soluble in ethyl alcohol, benzene, ether, or ethyl acetate, and only sparingly so in cold light petroleum (b. p. 30–50°).

It is moderately stable, differing in this respect markedly from desylamine; thus a specimen kept in a well-corked tube underwent no apparent change when kept for six days. It then became yellow, the crystals adhered together, and after a further four to five days it was transformed into a yellowish-brown, semi-liquid mass.

In another preparation where 15 grams of the phthalamic acid were hydrolysed by heating for half an hour with 60 c.c. of hydrochloric acid and 100 c.c. of glacial acetic acid, the yield of amino-ketone (2.5 grams) was better than in the experiment just described.

The *picrate* crystallises from ethyl alcohol in yellow leaflets (Found, $N=12.4$. $C_{15}H_{15}ON, C_6H_3O_7N_3$ requires $N=12.3$ per cent.), which commence to darken and sinter at 175°, and melt and decompose at 193°.

The *platinichloride* separates from dilute hydrochloric acid in brown needles (Found, $Pt=22.5$. $(C_{15}H_{15}ON)_2H_2PtCl_6$ requires $Pt=22.7$ per cent.). It shows no definite melting point, but commences to darken and shrink to a thin core at 195°, decomposition being complete at 250°.

The crude β -amino- β -phenylpropiophenone hydrochloride resulting from the hydrolysis of the phthalamic acid was shaken with benzoyl chloride and sodium hydroxide. The resulting solid was crystallised from ethyl alcohol, from which it separated in needles melting at 152–153°. This was identical with the benzoyl derivative previously described (p. 73) obtained by the interaction of β -benzoylamino- β -phenylpropionyl chloride and benzene in the presence of aluminium chloride.

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