[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Action of Grignard Reagents on Heterocyclic Compounds. I. Action of Grignard Reagents on Unsaturated Azlactones

WILLIAM IBRAHIM AWAD AND MOHAMED SHAWKEY HAFEZ

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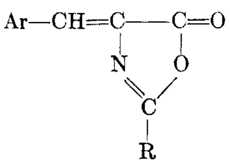
Phenylmagnesium bromide reacts with unsaturated azlactones (I) to give carbinols (II), and in some cases the corresponding oxazoline (III) has been isolated. The oxazolines have also been obtained from the corresponding carbinol by the action of an acetic anhydride–sodium acetate mixture. Both the carbinols (II) and the oxazolines (III) have been transformed by the action of a hydrochloric acid–acetic acid mixture to give compounds of structure (V). The constitution of the products is discussed.

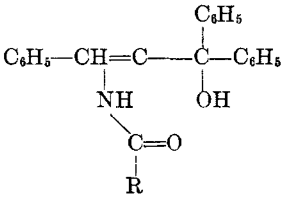
Recently Pourrat,[1] Mustafa and Harhash,[2] and Filler and Wismar,[3] have investigated the action of some Grignard reagents on unsaturated azlactones. The results of these investigators differed in several instances. We have now reinvestigated the whole problem.

Phenylmagnesium bromide reacts with 2-phenyl-4-benzylidene-5(4H)-oxazolone (Ia), to give mainly 1,1-diphenyl-2-benzamidocinnamyl alcohol (IIa) as described by Mustafa and Harhash[2] (the melting point of IIa is similar to that described by Filler and Wismar[3]). Contrary to the relative yields reported by Filler and Wismar,[3] only a small quantity of 2,5,5-triphenyl-4-benzylidene-2-oxazoline (IIIa)(m.p. 176°, Filler and Wismar[3] 161–163°; Pourrat[1] 151°) was isolated together with IIa on working with high concentrations.



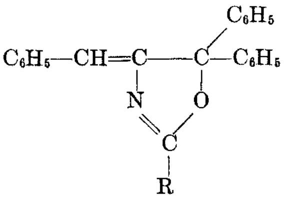
I

Ia. Ar = R = C_6H_5
Ib. Ar = C_6H_5, R = CH_3



II

IIa. R = C_6H_5
IIb. R = CH_3



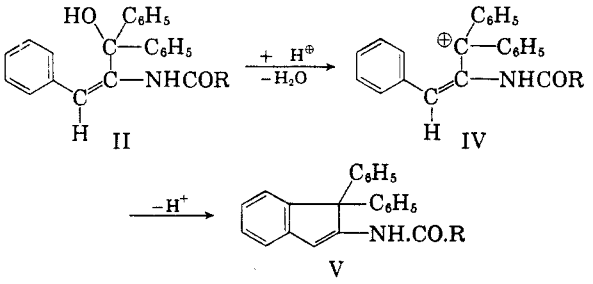
III

IIIa. R = C_6H_5
IIIb. R = CH_3

Mustafa and Harhash[2] reported that refluxing IIa with an acetic acid–hydrochloric acid mixture gave a compound (m.p. 186°) to which they erroneously gave structure IIIa. Filler and Wismar[3] failed to reproduce this experiment. These authors attributed the difference between Mustafa and Harhash[2] and Pourrat[1] regarding this compound to stereochemical factors.

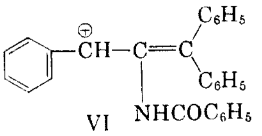
Attempts to prepare the above compound, m.p. 186°, under the conditions mentioned by Mustafa and Harhash[2] were not successful. However, when the experiment was repeated in the cold or by mere warming the compound was obtained in almost quantitative yield.

The constitution of this product is believed to be 1,1-diphenyl-2-benzamidoindene, Va, formed according to the following scheme.

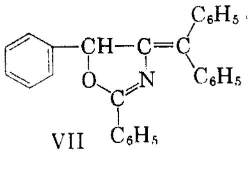


Va. R = C_6H_5
Vb. R = CH_3

It was thought at the beginning of this study that the carbonium ion (IV) isomerized to VI, which readily cyclized to give VII.



VI



VII

Ozonolysis of the product did not give any benzophenone but mainly a high melting pale yellow compound.

The constitution of V is mainly based on: 1) oxidation with concentrated sulfuric acid and mercuric sulfate[4] to give phthalic anhydride, thus definitely excluding structure (VII); 2) the infrared spectrum of the product in carbon tetrachloride, showing an —NH stretching frequency at 3472

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(1) Pourrat, *Bull. Soc. chim. France,* 828 (1955).

(2) Mustafa and Harhash, *J. Org. Chem.,* **21,** 575 (1956).

(3) Rober Filler and James D. Wismar, *J. Org. Chem.,* **22,** 853 (1957).

(4) A. Schönberg, W. I. Awad, and G. A. Mousa, *J. Am. Chem. Soc.,* **77,** 3850 (1955).

cm.$^{-1}$, amide I at 1694 cm.$^{-1}$, and amide II at 1618 cm.$^{-1}$; 3) its colorlessness; and 4) the compounds being insoluble in hydrochloric acid (*i.e.*, it is not basic).

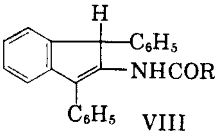
Compounds of structure III have been transformed to compounds of structure V by the action of a hydrochloric acid–acetic acid mixture.

$$\begin{array}{l}\text{IIIa. R} = C_6H_5 \\ \text{IIIb. R} = CH_3\end{array} \xrightarrow{H^+} \text{IV} \longrightarrow \text{V}$$

This reaction is in favor of the formation of the carbonium ion IV. The same product was obtained by boiling II in benzene in the presence of phosphorus pentoxide or by refluxing this carbinol in glacial acetic acid or formic acid.

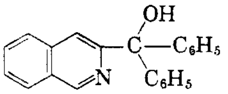
A Fischer model of the *cis* form of that carbinol (II) shows that the hydroxylated carbon is vicinal to the phenyl group on which the ring closure takes place. This cannot be taken as a criterion for the stereochemical configuration of that carbinol, as the formation of the carbonium ion IV and its possible canonical structure VI may cause a free rotation around the carbon atom attached to the phenyl group on which the ring closure has taken place.

The authors are in favor of structure V and not of structure VIII (by cyclization of the carbonium ion VI), because of the relative stability of the carbonium ion IV when attached to two phenyl groups (+E) as compared with the carbonium ion VI which is attached to one phenyl group.



VIII

One might argue that the ring closure results in an isoquinoline structure IX, which, in reality on oxidation can give phthalic anhydride. This structure is excluded on the following basis: 1) such a structure is basic in nature, a fact which is not present in the compound, and 2) infrared spectrum (*inter alia*).



IX

Trials to hydrolyze V by 70% sulfuric acid gave only a high melting compound which may be a polymer, as indenes are known to be easily polymerized.

The action of acetic anhydride and sodium acetate on IIa, which gave a yellow-brown product with a melting range (140–160°) as described by Filler and Wismar,[3] was reinvestigated. We have isolated from that product by elution chromatography on alumina, two compounds, a yellow product IIIa and a colorless product in a good yield, which proved to be Vb by melting point and mixture melting point.

Phenylmagnesium bromide was also allowed to react with 2-methyl-4-benzylidene-5(4H)-oxazolone (Ib) to give mainly 1,1-diphenyl-2-acetamidocinnamyl alcohol (IIb). When this compound was allowed to react with an acetic anhydride–sodium acetate mixture, only one product was obtained having structure IIIb, according to Filler and Wismar.[3]

When the carbinol IIb or the oxazoline IIIb is treated with a hydrochloric acid–acetic acid mixture, one and the same compound is obtained which is believed to be 1,1-diphenyl-2-acetamido-indene, Vb. This structure is deduced by analogy with Va and the infrared spectrum (an —NH stretching frequency at 3472 cm.$^{-1}$, amide I at 1697 cm.$^{-1}$, and amide II at 1623 cm.$^{-1}$).

EXPERIMENTAL

Microanalyses were carried out by Alfred Bernhardt, im Max Planck Institut, Mülheim (Rühr) Germany. The melting points are not corrected.

The infrared measurements are carried out in Perkin-Elmer infracord model 137 in carbon tetrachloride solution. Cell thickness 0.5 mm.

Reaction of 2-phenyl-4-benzylidene-5(4H)-oxazolone (Ia) *with phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide [prepared from 3.65 g. (0.15 g.-atom) magnesium turnings and 23.6 g. (0.15 mole) bromobenzene in 50 ml. ether], was added a fine suspension of 2-phenyl-4-benzylidene-5(4H)-oxazolone (12.5 g.) in 70 ml. ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath until nearly all the ether was driven off. The oily residue thus obtained was triturated with 50 ml. alcohol and allowed to cool. A colorless substance (IIa) separated, which was filtered (yield 11.95 g.), m.p. 165°. The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 83.23; H, 5.71; N, 3.34.

The mother-liquor was treated with a little water and left overnight. A yellow substance separated (IIIa) which was filtered and crystallized from ethyl alcohol in yellow crystals, m.p. 176° (yield 1.35 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{21}N\ O$: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.18; H, 5.71; N, 3.82.

Action of a hydrochloric acid-acetic acid mixture on carbinol IIa. To a fine suspension of IIa (1.0 g.) in acetic acid (20 ml.) was added hydrochloric acid (10 ml.) (sp. gr. 1.18). The substance went gradually into solution (yellow color). The reaction mixture was warmed on a water bath for 2 min. and left at room temperature for 30 min. A colorless substance separated: it was filtered, washed with water, and crystallized from benzene-petroleum ether (b.p. 40–60°) in colorless needles, m.p. 186° (yield 0.9 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{28}H_{21}N\ O$: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.56; H, 5.48; N, 3.54.

Action of acetic acid or formic acid on IIa. IIa (1.0 g.) was refluxed with acetic acid or formic acid (50 ml.) for 30 min. The acid was distilled and the volume was reduced to 10 ml. and allowed to cool. A colorless substance separated which was filtered, washed with water, and crystallized from benzene-petroleum ether (b.p. 40–60°) (yield 0.81 g.

in the case of acetic acid and 0.88 g. in the case of formic acid). The substance proved to be Va (melting point and mixture melting point).

Action of phosphorus pentoxide on IIa *in benzene.* To a solution of IIa (1.0 g.) in anhydrous benzene (50 ml.) was added phosphorus pentoxide (2 g.). The color changed immediately (orange-yellow). The reaction mixture was refluxed for 30 min., filtered, and concentrated; a colorless product separated. It was filtered and crystallized from benzene-petroleum ether (b.p. 40–60°) as colorless needles, (yield 0.84 g.). This product proved to be Va (melting point and mixture melting point).

Action of acetic anhydride and sodium acetate on IIa. IIa (4 g.) was refluxed with acetic anhydride (200 ml.) and fused sodium acetate (2.0 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. The yellowish-brown substance thus obtained (m.p. 140–160°) was treated with 50 ml. of ethyl alcohol and warmed on a water bath. A yellow substance separated which was filtered and crystallized from ethyl alcohol as yellow flakes [m.p. 176°, undepressed on admixture with IIIa (yield 0.45 g.)]. The mother-liquor was treated with little water and left overnight. A colorless substance separated, m.p. 140–145° (yield 2.7 g.). Elution chromatography of this substance over alumina using ether as eluent gave a colorless substance which was crystallized from petroleum ether (b.p. 60–80°) as colorless fluffy needles, m.p. 185° (undepressed on admixture with Vb).

The acidic aqueous layer was extracted with ether several times. The combined ethereal extract was washed with a little water, dried over anhydrous sodium sulfate, and evaporated on a water bath. A colorless substance separated (0.9 g.), which was shown to be benzoic acid (melting point and mixture melting point).

Action of a hydrochloric acid–acetic acid mixture on oxazoline (IIIa). The experiment was carried out as described before for the carbinol IIa. The product was shown to be Va (melting point and mixture melting point).

Ozonolysis of Va.[5] A stream of ozonized oxygen was allowed to pass through a solution of Va (2 g.) in chloroform (100 ml.) for 15 min. The reaction mixture was hydrolyzed with water. The chloroform solution was then extracted with a dilute solution of sodium carbonate, then washed with water. The chloroform layer was separated and concentrated: a solid separated which melted above 300°. Acidification of the carbonate solution gave a colorless substance which was filtered and crystallized from water and proved to be benzoic acid (melting point and mixture melting point).

Oxidation of Va *to phthalic anhydride.* A mixture of Va (0.5 g.), mercuric sulfate (0.3 g.), and concd. sulphuric acid (4 ml.) was placed in a glass retort (100 ml. capacity). The mixture was then heated in a metal bath for 10 min. at 250° (bath temperature), then for 50 min. at 300–310° (bath temperature), after which colorless needles were observed on the colder part of the retort tube. The crystals were scratched out of the tube and sublimed to give the characteristic needles of phthalic anhydride (melting point and mixture melting point and positive fluorescein test).

Reaction of 2-methyl-4-benzylidene-5(4H)oxazolone (Ib) *with phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide [prepared from 3.65 g., (0.15 g.-atom) of magnesium turnings and 23.6 g. (0.15 mole) of bromobenzene in 50 ml. ether], was added a fine suspension of 2-methyl-4-benzylidene-5(4H)oxazolone (9.35 g.) in 70 ml. of ether. The reaction mixture was treated as in the case of Ia. The oily residue thus obtained was triturated with petroleum ether (b.p. 60–80°) and allowed to cool. A colorless substance separated which was filtered and crystallized from benzene as colorless needles, m.p. 147° (yield 10.5 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.35; H, 6.06; N, 4.31.

Action of a hydrochloric acid–acetic acid mixture on IIb. To a fine suspension of IIb (1.0 g.) in acetic acid (20 ml.) was added hydrochloric acid (10 ml.) (sp. gr. 1.18). The substance went gradually into solution (yellow color). The reaction mixture was treated as in the case of IIa. The product was crystallized from petroleum ether (b.p. 60–80°) in colorless needles, m.p. 185° (yield 0.91 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.82; H, 6.16; N, 4.24.

Action of acetic anhydride and sodium acetate on IIb. IIb (1.0 g.) was refluxed with acetic anhydride (50 ml.) and fused sodium acetate (0.5 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. A pale-yellow substance (Vb) separated which was filtered, washed with water, and crystallized from ethyl alcohol as very pale yellow needles, m.p. 97° (yield 0.85 g.). The substance gave an orange color with concd. sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.70; H, 6.12; N, 4.32.

Action of a hydrochloric acid–acetic acid mixture on oxazoline (IIIb). The experiment was carried out as described before for IIb. The product proved to be Vb (melting point and mixture melting point).

ABBASSIA, CAIRO, EGYPT, U. A. R.

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(5) The authors wish to express their thanks to Professor G. Soliman, Alexandria University, for allowing them to use the ozonizer at his disposal.