THE STRUCTURE AND GRIGNARD REACTION OF THE β-AMINOCROTONONITRILE¹

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ABSTRACT

The ultraviolet absorption spectra of the low and high melting forms of β aminocrotononitrile (I) provide evidence that both of them possess the same enamine structure. Since the existence of the polymorphic modifications of I must be excluded on the basis of the thermochemical behavior of I, the difference of the two modifications is capable of accounting for *cis* and *trans* isomerism, the low melting modification being the *cis* form, and the high mélting modification being the *trans* form.

In the reaction of I with aromatic Grignard reagents β -amino ketones of the type CH₃-CO-CH=C(NH₂)-R are formed as the main reaction products. The free radical mechanism of the formation of I is postulated.

INTRODUCTION

The treatment of acetonitrile (3) and propionitrile (7) with sodium in the absence of a solvent gives aminopyrimidine derivatives. However, in benzene solution sodium produces with acetonitrile the β -aminocrotononitrile (I) (9), and propionitrile gives 3-amino-2-methyl-2-pentenenitrile (II) (10, 11). The same type of condensation occurs between acetonitrile and aromatic nitriles (11, 13, 14, 16), or higher aliphatic nitriles (15, 18).

von Meyer (13) obtained I in the form of two crystalline modifications: the low melting $(52-53^{\circ})$ modification having the higher solubility in benzene, and the high melting $(79-83^{\circ})$ modification having the lower solubility in benzene. von Meyer postulated the ketimine-enamine tautomerism of this substance. However, he did not give any proof of this idea. Although I is a versatile reagent in organic synthesis, the structure of the two modifications of I is not known as yet.

The objective of this work was twofold: firstly, to study the properties of I to elucidate the nature of the two modifications, and secondly, to find out whether the Grignard reaction of I could serve as a preparative method for the synthesis of β -amino ketones.

DISCUSSION

Mechanism of Formation

The chemical equations of the formation of I from acetonitrile and sodium, as they were given by von Meyer (10) and Holtzwart (9) did not represent a detailed mechanism of the reaction. Therefore we propose a new mechanism of formation of β -aminocrotononitrile involving free radical intermediates (Chart I). In the primary interaction a free methyl radical is formed. The free methyl radical extracts a hydrogen atom from the second molecule of aceto-

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nitrile, forming methane and the free \cdot CH₂CN radical. This radical attacks the third molecule of acetonitrile to form the free β -aminocrotononitrile radical, which reacts with the second atom of sodium to produce the sodium salt of β -aminocrotononitrile. This mechanism could apply equally well to the reaction of other aliphatic nitriles with sodium in benzene solution.

The Ultraviolet Absorption

The ultraviolet absorption spectra of both the modifications of I were determined in absolute ethanol and acetonitrile in the region from 220 to 295 m μ . In both solvents, the absorption curves were symmetrical with only

one well defined maximum at almost the same wave length for both modifications (Table I), (Figs. 1 and 2).

The observed ultraviolet absorption indicates that both the modifications of I have identical electronic configuration when dissolved in polar solvents, and therefore the existence of the tautomeric forms of I must be excluded. The spectra are in accordance with the enamine structure of I, in which the

TABLE I

Ultraviolet absorption spectra of β -aminocrotononitrile				
1	Absolute ethanol		Acetonitrile	
	λ_{max}	εmax	λ _{max}	ε _{max}
Low melting modification	258 mµ	13600	254.5 mµ	12430
High melting modification	256 mµ	14700	254.5 mµ	13650



CONCENTRATION 0.0001 MOLAR IN ABSOLUTE ETHANOL

conjugation of the carbon-carbon double bond and cyano group, and the interaction of the amino group gives rise to the molar extinction coefficients and the shift of the λ_{max} towards the longer wave lengths, comparing the ultraviolet absorption of I with that of butyronitrile (λ_{max} 180 m μ) and acrylonitrile (λ_{max} 250 m μ) (4). The enamine form of I can exist as a resonance hybrid of three resonating structures I \leftrightarrow Ia \leftrightarrow Ib, two of them being ionic (Ia, Ib).



Heats of Melting and Solution

It is known that in an ideal solution, the heat of solution of a solid is identical with its heat of melting at the same temperature (17).

Rough values for the heats of melting of the two modifications of I are therefore given by the heats of solution of the two modifications in benzene, assuming ideal conditions for the solutions. Knowing the melting points of the two modifications, and their solubilities at 16.5° , it is possible to obtain the solubility curves for the two modifications. The plot of the mole fraction versus the inverse of the absolute temperature is a straight line (Fig. 3). The



heats of solution are obtained by multiplying the intercept by the term 2.303 RT. It is found that the values of the heats of solution of the two modifications, at the melting point, are identical within experimental limits of error (Chart III). It is quite safe to assume that the heats of melting of the two modifications will be of the same order of magnitude, and almost identical to each other.

CHART III

Calculation of heats of solution and heats of fusion of β -aminocrotononitrile MODIFICATIONS

Data for solubility curves of benzene solutions of β -aminocrotononitrile Low Melting Modification:

> Solubility at 289.5°A. = 8.57 gm./100 gm. of benzene. Mole fraction of solute = 0.0755. Log mole fraction = -1.122. Inverse of absolute temperature = 0.00346. Melting point = $325^{\circ}A$. Inverse of absolute temperature = 0.00308. Log mole fraction = 0.0.

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High Melting Modification:

Solubility at 289.5°A. = 1.22 gm./100 gm. of benzene. Mole fraction of solute = 0.0115. Log mole fraction = -1.939. Inverse of absolute temperature = 0.00346. Melting point = $352-357^{\circ}A$.

Inverse of absolute temperature = 0.00280. Log mole fraction = 0.0.

Intercept for High Melting Modification = 9.10. Heat of solution = $9.10 \times 4.576 \times 325 = 13,500$ cal./mole.

Intercept for Low Melting Modification = 8.22. Heat of solution = $8.22 \times 4.576 \times 357 = 13,600$ cal./mole.

The heats of melting of enamine and ketimine tautomers would not be identical, with the result that such tautomers are ruled out as possible structures for the two modifications of I.

Polymorphic Modifications

The possibility of the two modifications of I being polymorphic modifications has been considered.

Enantiotropic polymorphism demands the existence of a transition temperature, above which one modification would be stable and the other modification would be reversed (8). That means that the two forms should be entirely interconvertible at some temperature below their melting points. Also, there should be only one melting point for the compound. No such transition temperature has been found for I, the lower melting modification being the stable modification at all temperatures. Both forms have definite melting points. These lines of evidence rule out the existence of enantiotropic polymorphism of I.

Monotropic polymorphism appears to be a likely possibility at first. Such polymorphism demands the existence of an imaginary transition temperature, that is, one which is above the melting points of the two modifications (8). One modification would be stable, and the other would be metastable at all times. There would be two melting points, one for each modification. Such stability and the two melting points were found in the case of I. However, the order of stability is the reverse of the expected one. The lower melting modification, if it is a polymorph of the monotropic type, should be the metastable form and should spontaneously transform into the higher melting modification. Investigation of the I has shown that the low melting modification is the more stable of the two modifications, and that the direction of transformation is from the high melting form to the low melting form. In addition, the heats of fusion of polymorphic modifications have been found to differ greatly. Because the heats of fusion of the two modifications of I were found to be nearly identical, the existence of monotropic polymorphism has been ruled out.

Cis and Trans Isomerism of I

Since the two possibilities to explain the existence of two modifications of I were excluded as a result of the present investigation, we propose that these

modifications are *cis* and *trans* isomers. The high melting form (79-83°) has been given the *trans* structure (III) by virtue of its higher melting point and lower solubility. The low melting form (52-53°) has been given the cis structure (IV) on the basis of its lower melting point and higher solubility. In the cis form, the amino and cyano groups are in adjacent positions, and can form an internal hydrogen bond (V), which would make the *cis* form more stable than the trans isomer. This means that irradiation of the lower melting form with ultraviolet light would not cause any transformation of the molecule into the higher melting form. The additional ionic structures Ia and Ib could influence the crystallization of I from organic solvents, From a nonpolar solvent, like benzene, both modifications can be easily crystallized without any changes. However, crystallization of these modifications from a polar solvent, like ethanol, produce only the low melting form. The explanation of this behavior is that in polar solvents, the contribution of the ionic structures Ia and Ib to the resonance hybrid would be greater than in a nonpolar solvent. The structures Ia and Ib do not possess the double bond of the enamine system, permitting the free rotation about the single bond between the α - and β -carbon atoms, and consequently, the change of the unstable modification into the stable one.

The Grignard Reaction

The Grignard reaction of I starts in the amino group by substituting both

of the hydrogen atoms by the MgX groups and the formation of two hydrocarbon molecules (15). Only if the threefold excess of the Grignard reagent is used the nitrile group is also attacked. In the reaction of I with aromatic Grignard reagents substituted β -amino ketones (VI, XIII-XVI), and β diketones were isolated as the final reaction products in varying yields.

Phenylmagnesium bromide and I gave the 4-amino-4-phenyl-3-butene-2one (VI). The structure of VI was evidenced by the fact that it gave with hydroxylamine hydrochloride 3-methyl-5-phenylisoxazole (IX) (6). The latter



compound could only be formed if the N=OH group, and therefore the carbonyl group of the β -amino ketone, was adjacent to the methyl group. As further proof of the position of the carbonyl group in VI, the β -phenylaminocrotononitrile (XVII) was reacted with phenylmagnesium bromide. The main reaction product was 1-amino-1-phenyl-3-phenylimino-1-butene (XVIII) which on hydrolysis with 75% sulphuric acid produced 4-amino-4-phenyl-3butene-2-one (VI).

The VI isolated in this investigation was an oil, boiling at 70-80° at 1 mm. of pressure. The boiling point of VI was not in agreement with physical properties of the two isomer amino ketones prepared by Claisen (5). The latter compounds were 4-amino-4-phenyl-3-butene-2-one, melting point 86-87°, and 3-amino-1-phenyl-2-butene-1-one, melting point 143° (VIII).

The fact that two compounds have been identified as having the structure VI is believed to be due to the cis-trans isomerism, as shown by the formulae X and XI. The amino ketone, boiling point 70-80° at 1 mm., is assumed to be the cis form, because it has the lower melting point of the two known isomers. The substance, isolated by Claisen (5), is given the trans configuration. The cis isomer can be stabilized by the hydrogen bond (XII), as in the case of the enol forms of β -diketones.

The presence of the carbon-carbon double bond and exclusion of other possible structures for the obtained substance VI is evident from the following considerations. The failure of the VI to give a positive test with ferric chloride solution indicates that there is no enol formation. The β -ketimino ketone structure (VII) was also excluded, since this structure cannot form any resonance forms, contrary to β -amino ketone structure which is stabilized by resonating ionic forms (VIa and VIb).

In the reactions of aromatic Grignard reagents with I, 1-phenyl-1,3-butanedione (XX) and 1- α -naphthyl-1,3-butanedione (1) (XXI) were isolated in yields of 5–10%. It is evident that these β -diketones were formed by hydrolysis of the corresponding β -amino ketones, VI and XIII respectively.

The reaction of β -amino nitriles with Grignard reagents was extended to include the 3-amino-2-methyl-2-pentenenitrile (II). This substance gave with phenylmagnesium bromide 1-amino-2-methyl-1-phenylpentene-3-one (XIX).

EXPERIMENTAL*

Preparation of β -Aminocrotononitrile (I) (13).

The main feature of the preparation of the two modifications of I is the decomposition of the sodium salt of I with water at different temperatures. The low melting modification is obtained if the decomposition of the salt is carried out at 30° . The preparation of the high melting modification requires the use of ice-cold water. In both cases I is extracted from the reaction mixture with ether. After the evaporation of ether at reduced pressure the crystalline residues are recrystallized from benzene.

Since both modifications of I did not show any difference in reactions with other substances, the low melting modification was only used in the study of the Grignard reaction of I.

Ultraviolet Absorption Spectra

Ultraviolet absorption spectra were obtained using a Beckman quartz spectrophotometer model DU. The solvents, ethanol and acetonitrile, were purified by the standard methods.

Reaction of I with Phenylmagnesium Bromide

Ten grams (0.15 mole) of I dissolved in 100 ml. of ether were added with stirring to a solution of 0.5 mole of phenylmagnesium bromide in 300 ml. ether over a period of 10 min. A dark oil separated from solution. The mixture was then refluxed for six hours.

(a) 4-Amino-4-phenyl-3-butene-2-one (VI)

The Grignard complex was decomposed by the gradual addition of an icecold saturated aqueous animonium chloride solution. The ether layer was separated and the aqueous solution was extracted with ether. The combined ether extract was dried and distilled under reduced pressure to yield VI as a light colorless oil, boiling at 70–80° at 1 mm. pressure. The yield was 5.0 gm. (20%).

The 2,4-dinitrophenylhydrazone of VI, crystallized from benzene as orange needles, melting point 241-242°.

* Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Anal. calc. for C₁₆H₁₅N₅O₄: C, 56.30; H, 4.40; N, 20.53%. Found: C, 56.28; H, 4.29; N, 20.40%.

3-Methyl-5-phenylisoxazole (1X).—A mixture of 0.5 gm. of VI, 0.5 gm. of hydroxylamine hydrochloride, and 2.0 gm. of potassium hydroxide in 5 ml. of water were refluxed for two hours. The reaction product IX was recrystallized from alcohol as white needles, melting at 67°, lit. (6) m.p. 67–68°. Anal. calc. for C₁₀H₉NO: N, 8.81%. Found: N, 8.70%.

(b) 1-Phenyl-1,3-butanedione (XX)

(α).—Following decomposition of the Grignard complex and extraction with ether, the alkaline aqueous solution was neutralized with hydrochloric acid and cooled. A precipitate of XX was removed by filtration and recrystallized from ethanol as white needles, melting at 60–61°; lit. (6). The yield was 1 gm. (5%).

(β).—The ether solution of the decomposed Grignard complex was repeatedly extracted with 20 ml. portions of saturated sodium bicarbonate solution until the aqueous portion was colorless. The bicarbonate solution was acidified with hydrochloric acid, and cooled in ice. The crystalline precipitate was recrystallized from ethanol as white needles, m.p. 60–61°. The yield was 2.0 gm. (10%).

Reaction of hydroxylamine with XX.—The XX was treated with hydroxylamine hydrochloride in a procedure similar to that described previously, and IX was obtained as white needles, m.p. $66-67^{\circ}$.

Anal. calc. for C₁₀H₉NO: N, 8.81%. Found: N, 8.72%.

Reaction of I with α -Naphthylmagnesium Bromide

Ten grams (0.15 mole) of I and 0.5 mole of α -naphthylmagnesium bromide were reacted in a procedure similar to that described in the reaction of phenylmagnesium bromide. The residue which was obtained by the evaporation of the ether extract was steam-distilled to remove naphthalene produced by the reaction of the Grignard reagent with the active hydrogen of I. Following the steam distillation, the residue was extracted with ether.

(a) 4-Amino-4- α -naphthyl-3-butene-2-one (XIII)

The dried ether extract was distilled under reduced pressure, yielding 6.5 gm. (25.2%) of a light oil, boiling at $130-135^{\circ}$ at 1 mm.

Anal. calc. for C14H13NO: N, 6.48%. Found: N, 6.30%.

The 2,4-dinitrophenylhydrazone of XIII was recrystallized from benzene as fine orange needles, m.p. 216-217°.

Anal. całc. for C₂₀H₁₇N₃O₄: C, 61.38; H, 4.35; N, 17.90%. Found: C, 61.44; H, 4.14; N, 17.61%.

The semicarbazone of XIII had the m.p. 213-214° (white plates from ethanol).

Anal. calc. for C15H16N4O: N, 20.90%. Found: N, 20.76%.

Reaction of hydroxylamine with XIII gave 3-methyl-5- α -naphthylisoxazole (IX) as white plates crystallized from ethanol, m.p. 140–141°.

Anal. calc. for C₁₄H₁₁NO: N, 6.70%. Found: 6.82%.

(b) $1-\alpha$ -Naphthyl-1,3-butanedione (XXI)

The ether extract of the decomposed Grignard complex was repeatedly extracted with saturated bicarbonate solution. The latter was neutralized with hydrochloric acid, and cooled. The precipitate was recrystallized from ethanol as fine prisms, melting at $107-108^{\circ}$. The yield was 1.5 gm. (5.8%).

Anal. calc. for C₁₄H₁₂O₂: C, 79.25; H, 5.66%. Found: C, 79.27; H, 5.60%.
4-Amino-4-o-tolyl-3-butene-2-one (XIV).—This substance was prepared from o-tolylmagnesium bromide and I. It was a light yellow oil, boiling at 40-50° at 4 mm. The yield was 2.5 gm. (11%).

The 2,4-dinitrophenylhydrazone of XIV, orange needles, melting at 162-163°.

Anal. calc. for C₁₇H₁₇N₅O₄: C, 57.46; H, 4.79; N, 19.72%. Found: C, 57.81; H, 4.25; N, 19.41%.

4-Amino-4-p-tolyl-3-butene-2-one (XV).—It was obtained in the reaction of p-tolylmagnesium bromide and I. XV was a yellow oil, distilling at $30-40^{\circ}$ at 4 mm. The yield in several preparations varied from 2.5 to 3.2 gm. (11-15%).

The 2,4-dinitrophenylhydrazone of XV, fine red needles from benzene, m.p. 259-260°.

Anal. calc. for C₁₇H₁₇N₅O₄: C, 57.46; H, 4.79; N, 19.72%. Found: C, 57.62; H, 4.58; N, 19.65%.

4-Amino-5-phenyl-3-pentene-2-one (XVI).—This compound was synthesized from I and benzylmagnesium bromide. It was a yellow oil, distilling at 70-75° at 1 mm. The yield was 3.5 gm. (16%).

The 2,4-dinitrophenylhydrazone of XVI, orange needles from benzene, m.p. 146-147°.

Anal. calc. for C₁₇H₁₇N₅O₄: C, 57.46; H, 4.79; N, 19.72%. Found: C, 57.53; H, 4.78; N, 19.62%.

1-Amino-1-phenyl-3-phenylimino-1-butene (XVIII).—The reaction between 19.2 gm. of XVII and 0.75 mole of phenylmagnesium bromide in 400 ml. ether was carried out for 48 hr. The reaction mixture was decomposed with ammonium chloride solution and extracted with ether. After evaporation of ether the residue was distilled under reduced pressure. The first fraction, boiling at 50-80° at 3 mm., was aniline (3.5 gm.). Distillation was stopped at this point, and the residue was crystallized from alcohol. The XVIII formed yellow crystals, m.p. 85-86°. The yield was 6.5 gm. (12%).

Anal. calc. for C₁₆H₁₆N₂: C, 81.36; H, 6.78; N, 11.86%. Found: C, 81.59; H, 6.70; N, 11.75%.

Acid hydrolysis of XVIII with 75% sulphuric acid at $150-160^{\circ}$ for one hour yielded VI, which was identified by its 2,4-dinitrophenylhydrazone, m.p. $241-242^{\circ}$. The hydrazone was also analyzed quantitatively.

Anal calc. for $C_{16}H_{15}N_5O_4$: C, 56.30; H, 4.40; N, 20.53%. Found: C, 56.22; H, 4.16; N, 20.26%.

1-Amino-2-methyl-1-phenyl-1-pentene-3-one (XIX).—In the reaction between 20.7 gm. of II and 0.6 mole of phenylmagnesium bromide in 400 ml. ether, 5.2 gm. (15%) of XIX was obtained as a light oil distilling at $80-90^{\circ}$ at 8 mm.

The 2,4-dinitrophenylhydrazone of XIX was crystallized from benzene as bright orange needles, m.p. 230-231°.

Anal. calc. for C₁₈H₁₉N₅O₄: N, 18.97%. Found: N, 18.68%.

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