The Condensation of Ethyl Phenylpropiolate with 3-Pyridylacetonitrile

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The reaction of 3-pyridylacetonitrile with ethyl phenylpropiolate gave not only the expected 3-hydroxy-5-phenyl-2-(3-pyridyl)pent-2-en-4-ynenitrile (IX) but also a di-Michael addition product of one molecule of the pyridylacetonitrile and two molecules of the acetylenic ester, ethyl 4-carbethoxy-3,5-diphenyl-6-(3-pyridyl) anthranilate (IV). Moreover, 2-ethoxy-6-phenyl-3-(3-pyridyl)pyrid-4-one (XIV) was also isolated as the cyclization product obtained after the addition of a molecule of ethanol to compound IX. Ir and nmr spectra are reported for all products.

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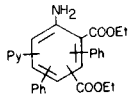
In the course of our study of the condensation reactions of acetylenic esters with compounds having active methylene groups, the condensation of ethyl phenylpropiolate with arylacetamides, acetonitriles and acetates have been carried out (1,2). Moreover the condensation of acetylenic esters with pyridyl compounds having active methylene groups such as ethyl 2-pyridylacetate indicated that the nature of the reaction product was different from that obtained from the corresponding arylacetates. The main reaction product obtained in the former case was identified as 4-quinolizone derivatives (3), and acetylenic β-keto esters were considered as the main reaction product in the latter case (2). In an extension of this work we now report the results obtained from the condensation of the acetylenic ester with 3-pyridylacetonitrile on which three different reaction products were obtained.

The first reaction product which was obtained in nearly 45% yield had a molecular formula of $C_{29}H_{26}N_2O_4$ according to elemental analyses. The nmr spectrum showed two carbethoxy groups in different environments. The broad signal at 5.0 τ which integrated for two protons and was exchangeable with deuterium oxide suggested the presence of a primary amino group. In addition, the spectrum showed multiplet signals in the aromatic region and integrated for fourteen protons (Table I). In the ir spectrum the presence of two absorption bands at 3500 and 3400 cm^{-1} confirmed the presence of a primary amino group. Furthermore the presence of two strong absorption bands at 1710 and 1690 cm^{-1} for the compound dissolved in chloroform gave further support for the presence of two carbethoxy groups in different environments (4). The ir spectrum of the above compound in the solid phase gave some evidence that one of the ester groups was hydrogen bonded to a neighboring amino group (Table I). The above spectral values are similar to a certain extent to those of *o*- and *p*-aminobenzoates (XVI and XVII, respectively) (Table I).

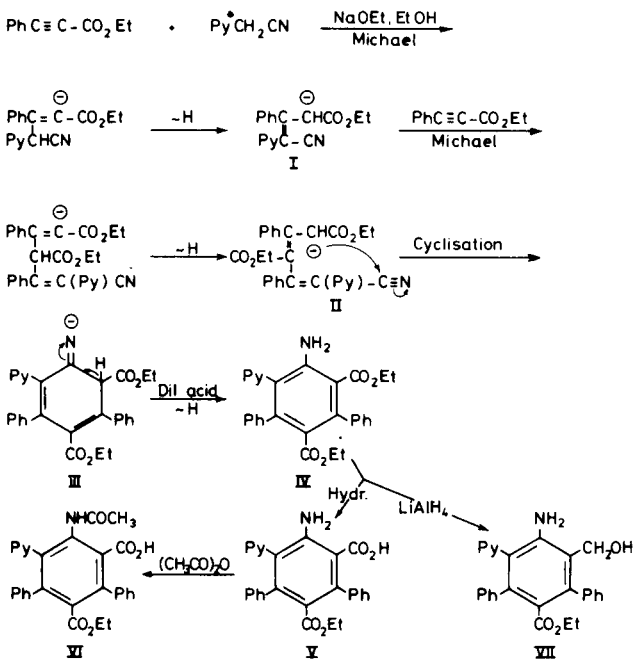
Accordingly, the structure of the reaction product under study could be crudely represented as:



The above product is probably the outcome of the condensation of one molecule of 3-pyridylacetonitrile with two molecules of ethyl phenylpropiolate (Scheme I). The first step involves a Michael addition of the pyridylacetonitrile to the acetylenic ester, followed by rearrangement to give the anion I. The second step involves a Michael addition of the anion I to a second molecule of the acetylenic ester followed by another rearrangement to give the anion II. Cyclization of II at the nitrile group would give the anion III which, upon acidification with dilute acid and aromatization, would give the product IV.

To get further information about the structure of compound IV, hydrolysis was carried out with dilute alkali and the hydrolysed product was identified as the monocarboxylic acid derivative (V). The nmr spectrum of V showed signals due to one ethyl group only which was in fact the one that absorbed at higher field in the original compound IV. Furthermore the ir spectrum of compound V lacks the higher wave number carbonyl ester absorption. Accordingly, the ester group which is *ortho* to the amino group is in fact the one which was hydrolysed and the

SCHEME I

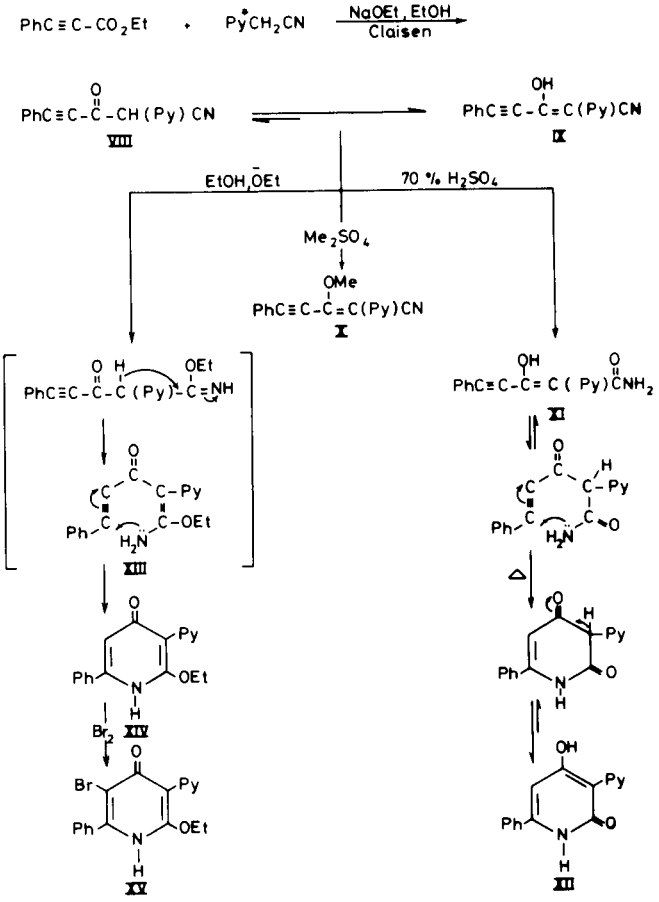


Py* = 3-Pyridylacetonitrile.

compound was identified as substituted anthranilic acid (V). Acetylation of the acid (V) afforded the acetanilide derivative (VI). Moreover, reduction of compound IV with lithium aluminium hydride gave the alcohol VII. From the nmr and ir spectral data of the alcohol (VII) (Table I), and as mentioned for the hydrolysis of compound IV, it is clear that the anthranilate ester group is again the one which is in fact reduced. According to the above reactions of compound IV it is concluded that as the anthranilate part of the molecule is the reactive center toward different reagents, the ester group which is *para* to the amino group is rather inert.

The nature of the second reaction product IX which was obtained in 16.2% yield, was similar to the one isolated from the reaction of ethyl phenylpropiolate with arylacetonitriles (1). In the latter case the product, which was a simple Claisen addition, was considered to be the main reaction product. The ir and nmr spectra of compound VIII indicated that it is present in the enol form (Table I) and therefore the product was assigned as IX (Scheme II). Methylation of compound IX with dimethyl sulphate gave the enol ether X, singlet at 6.17 τ was assigned to the methyl protons of the enol ether (Table I). Moreover hydrolysis of compound IX with 70% sulphuric acid

SCHEME II



Py* = 3-Pyridylacetonitrile.

afforded the intermediate acetylenic amide compound XI as shown from its nmr and ir spectra (Table I). It was noticed that during melting point determination of compound XI, the compound was solidified after melting at 188° and remelts again at 282-284°. The compound which melted at the latter temperature was tentatively identified as 3-(3-pyridyl)-4-hydroxy-6-phenylpyrid-2-one (XII) (Scheme II) (5). The ir spectrum of XII lacks the C≡C absorption present in the original compound XI and the nmr spectrum showed a signal at 3.4 τ which was assigned to the 5-H ethylenic proton.

The structure elucidation of the third reaction product which was obtained in 28.8% yield was also carried. Elementary analyses showed a molecular formula of $C_{18}H_{16}N_2O_2$ which differs from compound VIII by C_2H_6O. Accordingly attempts were focused toward the possible reaction product obtained from the addition of a molecule of ethanol to compound VIII. As the ir spectrum (Table I) showed no absorptions due to C≡C and C≡N stretchings, therefore it is most likely that after addition of a molecule

Table I

Ir and Nmr Spectral Data

Compound	Phase	max/cm^{-1}	Solvent	τ Values	Proton Assignment (a)
IV	Chloroform Nujol	3500, 3400, 1710, 1690, 1600 3450, 3340, 3240, 1727, 1710, 1640	Deuteriochloroform	9.37 (t), 9.28 (t) 6.41 (q), 6.15 (q) 5.0 (broad) 3.0-1.4 (m)	CH_3 (6H) CH_2 (4H) NH_2 (2H) (b) ArH (14H)
V	Nujol	3480, 3380, 3220 1720, 1640, 1560	DMSO	9.35 (t) 6.45 (q) 5.74 (broad) 3.0-1.94	CH_3 (3H) CH_2 (2H) $\overset{+}{N}H_3$ (3H) (b) ArH (14H)
VI	Nujol	3400, 3300-2400, 1720, 1660, 1500	DMSO	9.4 (t), 8.44 (s) 6.42 (q) 4.0-1.0 (m)	CH_3 (6H) CH_2 (2H) ArH, NH (b), CO_2H (b) (16H)
VII	Chloroform	3600, 3480, 3400, 1720	Deuteriochloroform	9.4 (t) 6.5 (q) 7.0 (broad) 5.4 (broad) 3.0-1.4 (m)	CH_3 (3H) CH_2 (2H) OH (1H) CH_2, NH_2 (b) (4H) ArH (14H)
IX	Nujol	3400-2400, 2180, 1600, 1560, 1490	DMSO	2.98-0.98 (m)	ArH (9H), OH (1H) (b)
X	Chloroform	2190, 2165, 1600, 1510, 1380	Deuteriochloroform	6.17 (s) 3.27-0.96 (m)	CH_3 (3H) ArH (9H)
XI	Nujol	3400, 3180, 2158, 1670, 1550, 1150	DMSO	3.0-0.97 (m)	ArH (9H), OH (1H) (b) NH_2 (2H) (b)
XIV	Nujol	3200-2400, 1618, 1600, 1550, 1360	DMSO	8.87 (t) 6.0 (q) 4.04 (s) 3.53-1.93 (m) -0.3 (broad)	CH_3 (3H) CH_2 (2H) CH (1H) ArH (9H) NH (1H)
XV	Nujol	3200-2400, 1590, 1555, 1345, 1150	DMSO	8.87 (t) 5.9 (q) 3.34-1.67 (m) -0.3 (broad)	CH_3 (3H) CH_2 (2H) ArH (9H) NH (1H)
XVI	Chloroform	3510, 3400, 1690, 1620, 1590	Deuteriochloroform	4.3 (broad)	NH_2 (b)
XVII	Chloroform	3510, 3410, 1700, 1630, 1610	Deuteriochloroform	5.9 (broad)	NH_2 (b)

(a) ArH represent protons of the phenyl and pyridyl groups. (b) Protons exchangeable with deuterium oxide.

of ethanol to the nitrile group of compound VIII the resulting intermediate XIII spontaneously cyslised at the acetylenic bond to give compound XIV (Scheme II). More evidence on the structure of compound XIV was obtained from its nmr spectrum (Table I) which showed the following signals: triplet and quartet at 8.87 and 6.0 τ respectively (due to ethoxy group), sharp singlet at 4.07 τ (due to ethylenic proton), multiplets between 3.5-1.9 τ (due to nine protons of aryl and pyridyl groups) and a broad signal at -0.3 τ (exchangeable with deuterium oxide) due to the NH proton (6). Bromination of compound XIV with a chloroform solution of bromine afforded the 5-bromo derivative XV (7). The nmr spectrum of the latter compound lacks the ethylenic proton which appeared in the spectrum of compound XIV at 4.07 τ.

From the above discussion, the isolation of compound IV and XIV beside IX (which have the same nature as the one isolated from arylacetonitriles) could be attributed to the difference in the experimental conditions applied. Since a simple Claisen condensation product was obtained at room temperature in the case of the arylacetonitriles, such conditions did not work for the 3-pyridylacetonitrile

Table II

Analytical Results

Compound	Formula	M.p. °C	Calcd. (%)			Found (%)		
			C	H	N	C	H	N
IV	$C_{29}H_{26}N_2O_4$	158-160	74.68	5.58	6.01	74.76	5.82	5.96
V	$C_{27}H_{22}N_2O_4$	218-220	73.97	5.02	6.39	74.01	5.06	6.36
VI	$C_{29}H_{24}N_2O_5$	202-204	72.5	5.00	5.83	72.82	5.07	5.62
VII	$C_{27}H_{24}N_2O_3$	141-143	76.42	5.66	6.60	76.8	5.7	6.61
IX	$C_{16}H_{10}N_2O$	210 dec.	78.05	4.07	11.38	77.99	4.03	11.27
X	$C_{17}H_{12}N_2O$	215-217	78.46	4.62	10.77	78.15	4.77	10.41
XI	$C_{16}H_{12}N_2O_2$	186-188	72.73	4.55	10.61	72.48	4.46	10.36
XIV	$C_{18}H_{16}N_2O_2$	218-219	73.97	5.48	9.59	73.7	5.44	9.43
XV	$C_{18}H_{15}N_2O_2Br$	174-176 (dec. at 300)	58.22	4.04	7.55	58.25	4.29	7.15

and both Michael and Claisen addition products were isolated at the reflux temperature of ethanol.

EXPERIMENTAL

Ir spectra were measured with a Beckman IR 10 instrument and H nmr spectra were determined with a Varian T-60A instrument (tetramethylsilane as the internal standard). Microanalytical samples were analysed using a 185B HP CHN analyser and the results are tabulated in Table II. Melting points were determined on a kofler block and are uncorrected. The purity of all reaction products were checked by tlc.

Condensation of Ethyl Phenylpropiolate and 3-Pyridylacetonitrile.

A mixture of ethyl phenylpropiolate (10.0 g.) and 3-pyridylacetonitrile (5.0 g.) was added dropwise with stirring to a solution of sodium (1.2 g.) in ethanol (20 ml.). The reaction mixture, which turned deep red in color, was refluxed for five hours and left overnight at room temperature. The reaction mixture was treated with a saturated solution of sodium chloride and then extracted with ether. The ethereal extract was dried (sodium sulfate) and evaporated to give a thick oil (7.6 g.) which after trituration with cold ether gave 6.0 g. (44.8%, based on the weight of the propiolate) of ethyl 4-carbethoxy-3,5-diphenyl-6-(3-pyridyl)-anthranilate (IV). It was recrystallized from methanol and melted at 158-160°. The aqueous layer was acidified to *p*H 7 with acetic acid (10%) whereupon a yellow precipitate was separated and filtered off. This solid was recrystallized from ethanol to give 3.0 g. (16.2%, based on the weight of the starting acetonitrile) of 3-hydroxy-5-phenyl-2-(3-pyridyl)pent-4-yn-2-ene IX, m.p. 210° dec.

The filtrate was extracted with chloroform and the chloroform extracts were extracted with sodium bicarbonate and then washed with water. The chloroform layer was worked up to give 2.0 g. (28.8%, based on the weight of the starting acetonitrile) of 2-ethoxy-3-(3-pyridyl)-6-phenylpyrid-4-one (XIV). It was recrystallized from acetone and mleted at 218-219°.

4-Carbethoxy-3,5-diphenyl-6-(3-pyridyl)anthranilic Acid (V).

Compound IV (0.3 g.) was added to a solution prepared by the successive addition of methanol (3.0 ml.) and water (0.3 ml.) to sodium (0.2 g.). The mixture was refluxed for 1.5 hours, cooled and filtered. The white sodium salt thus formed was acidified with dilute sulfuric acid (10%) and then filtered to give 0.17 g. (89.47%) of compound V. It was recrystallized from methanol, m.p. 218-220°. The chloroform solution of the product formed a greenish copper complex when treated with an aqueous solution of copper acetate.

N-Acetyl-4-carbethoxy-3,5-diphenyl-6-(3-pyridyl)anthranilic Acid (VI).

A mixture of substituted anthranilic acid (V) (0.2 g.) and acetic anhydride (0.4 g.) was warmed on a water bath for forty minutes. The reaction mixture which was cooled and then poured into cold water was warmed for five minutes and then cooled again. The isolated shiny white solid product (0.18 g., 81.8%) was identified as VI and recrystallized from methanol, m.p. 202-204°.

5-Carbethoxy-4,6-diphenyl-3-(3-pyridyl)-2-aminobenzyl Alcohol (VII).

Compound IV (0.5 g.) in dry ether (100 ml.) was added dropwise, with stirring and under a nitrogen atmosphere, to a solution of lithium aluminium hydride (0.3 g.). The mixture was refluxed for one hour, acidified with dilute sulfuric acid (10%) and then extracted with ether. The ethereal extracts were worked up to give the alcohol (VII) as bright white crystals (0.4 g., 88.89%), m.p. 141-143° (from acetone).

3-Methoxy-5-phenyl-2-(3-pyridyl)pent-4-yn-2-enenitrile (X).

Compound VIII (0.2 g.) in 1% sodium hydroxide solution (30 ml.) was warmed for ten minutes with dimethyl sulphate (1 ml.) and then cooled. The yellow solid obtained was recrystallized from methanol to give 0.2 g. (95.24%) of compound X, m.p. 215-217°.

3-Hydroxy-5-phenyl-2-(3-pyridyl)pent-4-yn-2-enamide (XI).

A solution of compound VIII (0.2 g.) in 70% sulfuric acid (2 ml.) was refluxed for thirty minutes. The mixture was cooled, and excess dilute sodium hydroxide was added followed by extraction with ether. The aqueous layer was acidified to *p*H 6 and the yellow solid obtained was recrystallized from acetone to give 0.2 g. (95.24%) of compound XI, m.p. 186-188°. It was noticed that during the m.p. determination of compound XI, the compound solidified after melting and remelted again at 282-284°.

The latter product was tentatively identified as XII.

5-Bromo-2-ethoxy-6-phenyl-3-(3-pyridyl)pyrid-4-one (XV).

A chloroform solution of bromine (0.1 ml.) was added dropwise to a suspension of compound XIV (0.1 g.) in chloroform. The reaction mixture was stirred at room temperature for two

hours. The solid formed was filtered and recrystallized from methanol to give 0.12 g. (92.3%) of compound XV as a yellow solid, m.p. 174-176°. It decomposed at 300°.

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