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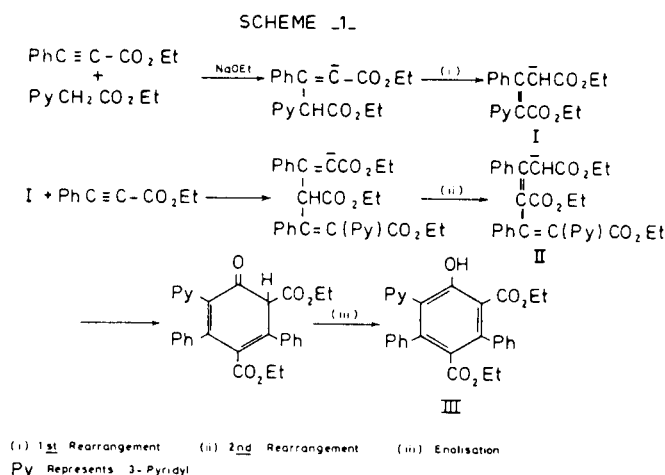
Ethyl phenylpropiolate reacted with ethyl 3-pyridylacetate in the presence of sodium ethoxide to give ethyl 3,5-diphenyl-4-carbomethoxy-6-(3-pyridyl)salicylate (III). Different derivatives for the product were prepared and their structures were elucidated on the basis of ir and nmr spectra.

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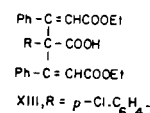
Recently we have reported a new method for the preparation of substituted 4-quinolizone from the reaction between ethyl phenylpropiolate and ethyl 2-pyridylacetate in the presence of sodium ethoxide (2). In this paper we report the use of ethyl 3-pyridylacetate in a similar condensation reaction where compound III was isolated and identified.

Elemental analyses of the reaction product under study indicated the molecular formula  $C_{29}H_{25}NO_5$ . The nmr and ir spectra (Table I) showed the presence of two carbomethoxy groups with different environments. The proton signal at 11  $\delta$  suggested the presence of enolic or strongly bonded proton (3). This was confirmed by the formation of deep violet coloration when the compound was treated with ferric chloride solution. In the ir spectrum, the presence of the absorption bands at 3600-2800 (broad), 1727 and 1664  $cm^{-1}$  gave further information that one of the ester groups might be engaged in hydrogen bonding with the neighboring OH group (4). Accordingly, we have chosen ethyl salicylate as a model molecule for comparison of the spectral values. With the exception of the absorption band at 1727  $cm^{-1}$ , the ir spectra of both the product and model compounds were comparatively similar. The presence of the ir band at 1727  $cm^{-1}$  and the appearance of a second ethyl signal in the nmr spectrum of the compound under study were considered as good evidence for the presence of a carbomethoxy group other than the one assigned to the salicylate part of the molecule. Up to this point and according to the elemental analyses and other nmr spectral values, the structure of the reaction product could be formulated as polysubstituted ethyl salicylate, the substituents being two phenyl groups, one pyridyl and one carbomethoxy group.

The latter product is most likely the outcome from the condensation between two molecules of ethyl phenylpropiolate and one molecule of ethyl 3-pyridylacetate (Scheme 1). The first step involves Michael addition of the pyridyl ester to the propiolate followed by rearrangement to give the anion I. The second step involves Michael addition of the anion I to a second molecule of the pro-

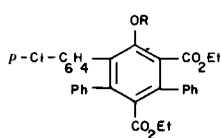


piolate followed by another rearrangement to give the anion II. Cyclisation of the latter anion followed by enolisation gave the product III. This reaction pathway is different from that reported for a similar condensation reaction between ethyl phenylpropiolate and ethyl arylacetates (5,6). In the latter case it was reported that the reaction was mainly proceeded by simple Claisen addition and the products were identified as acetylenic  $\beta$ -keto esters. In case of *m*-Cl, *p*-Cl and  $\alpha$ -naphthylacetates, the by-products which were obtained together with the corresponding  $\beta$ -keto esters were tentatively identified as the outcome of Michael addition between one mole of the acetate and two moles of the propiolate with subsequent hydrolysis of the acetate group. According to elemental analyses and molecular weight determination, the product from *p*-chloroacetate had a molecular formula  $C_{30}H_{27}ClO_6$  and the structure was tentatively assigned as XIII.



As the ir and nmr spectra of compounds XIII and III were to a certain extent similar to each other, it seems to us that the source of error in assigning structure XIII

compared with the corresponding one given for the pyridyl ester (III) was due to the presence of a molecule of water in XIII. Therefore the preparation of compound XIII was repeated and a pure sample was carefully dried under reduced pressure for several hours before subjected to elemental analyses. The new analyses results indicated that the molecular formula of compound XIII is in fact  $C_{30}H_{25}ClO_5$  which confirms that a molecule of water was in fact the source of error in the analytical results. Accordingly, this formula fits with the corresponding one presented for the product obtained from 3-pyridyl ester (III) and therefore the right structural formula for compound XIII could be represented as XIVa. Comparatively, similar results were obtained from the reaction between ethyl phenylpropiolate and 3-pyridylacetonitrile where ethyl 3,5-diphenyl-4-carbomethoxy-6-(3-pyridyl)anthranilate was isolated and identified (7).



XIV

a, R = H      b, R = CH<sub>3</sub>      c, R = COCH<sub>3</sub>

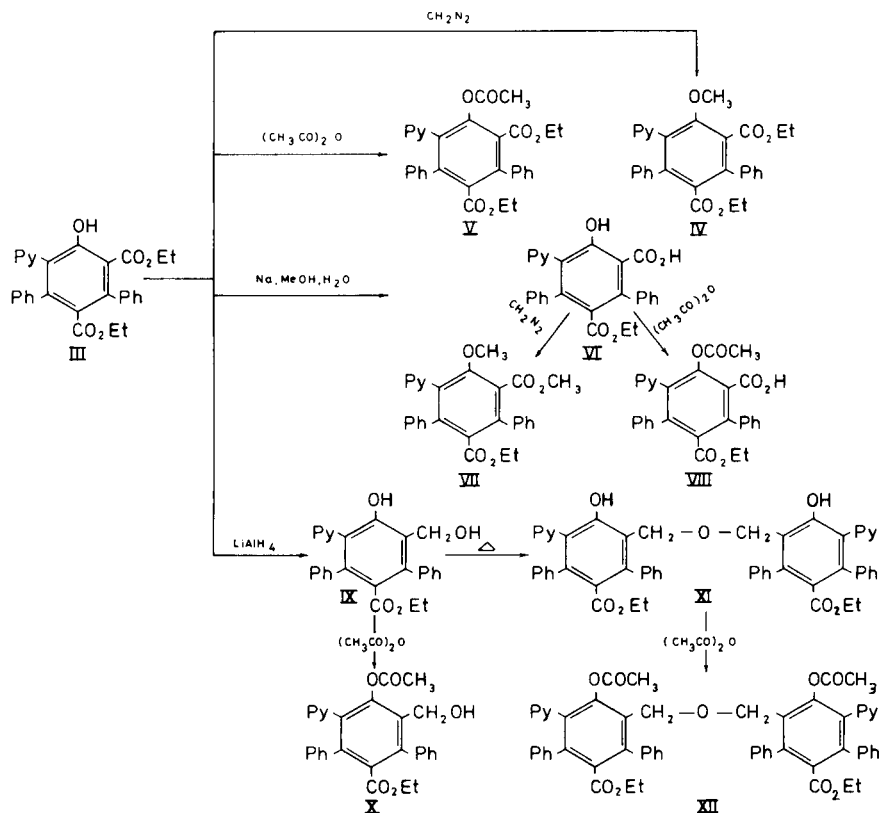
To get further information about the structure of compound III, the following derivatives and reactions were

carried out and identified (Scheme 2). Methylation of compound III with diazomethane gave the methoxy derivative IV. The nmr spectrum of IV showed a new methyl signal at 3.43  $\delta$  and lacks the phenolic OH signal at 11  $\delta$  present in the original compound. Similarly the ir spectrum showed only a strong carbonyl band at 1729  $cm^{-1}$  and again lacks the bands due to the bonded system present in the salicylate part of the original compound. The methoxy and acetoxy derivatives (XIVb and XIVc, respectively) of compound XIVa were prepared and identified on the basis of their analyses and spectral results (Tables I and II).

Hydrolysis of compound III with dilute alkali afforded the monocarboxylic acid derivative VI. The ir spectrum of VI showed that the salicylate ester group is in fact the one which was hydrolyzed. In addition, the nmr spectrum of VI gave further support to the hydrolyzed product (Table I). These spectral values were to a certain extent similar to those due to salicylic acid (Table I). Treatment of the acid VI with each of diazomethane and acetic anhydride gave compounds VII and VIII respectively. The spectral values of the latter compounds are tabulated in Table I.

Reduction of compound III with lithium aluminium hydride afforded the alcohol IX. Again, the ir and nmr spectral values showed that only the ester group which is *ortho* to the phenolic group is the one which is reduced

SCHEME 2.



Py Represents 3-Pyridyl.

TABLE I  
Ir and Nmr Spectral Data

Compound	$\nu$ max/cm <sup>-1</sup>		$\delta$	Protons (b)
III	3600-2800 (br)	OH-bonded	0.6 (t), 0.7 (t)	CH <sub>2</sub> (6H)
	1727 (vs)	C=O	3.4 (q), 3.8 (q)	CH <sub>2</sub> (4H)
	1664 (s)	bonded C=O	6.8-8.0 (m)	ArH (14H)
			11.0 (s)	ArOH (1H)
IV	1729 (vs)	C=O	0.66 (t), 0.9 (t)	CH <sub>3</sub> (6H)
			3.43 (s)	OCH <sub>3</sub> (3H)
			3.43 (q), 3.86 (q)	CH <sub>2</sub> (4H)
			6.9-8.0 (m)	ArH (14)
V	1770 (s) 1725 (vs)	C=O (OCOCH <sub>3</sub> ) C=O	0.67 (t), 0.85 (t)	CH <sub>3</sub> (6H)
			1.9 (s)	OCOCH <sub>3</sub> (3H)
			3.7 (q), 4.0 (q)	CH <sub>2</sub> (4H)
			7.1-8.6 (m)	ArH (14H)
VI (a)	3500-2500 1730	OH C=O	0.7 (t)	CH <sub>3</sub> (3H)
			3.2 (q)	CH <sub>2</sub> (2H)
			7.0-8.0 (m)	ArH, ArOH & CO <sub>2</sub> H (16H)
VII	1730 (vs)	C=O	0.67 (t)	CH <sub>3</sub> (3H)
			3.4 (s)	OCH <sub>3</sub> (3H)
			3.6 (s)	CO <sub>2</sub> CH <sub>3</sub> (3H)
			3.56 (q)	CH <sub>2</sub> (2H)
			7.0-8.6 (m)	ArH (14H)
VIII	3500-2800 (br) 1775 (s) 1730 (vs)	OH C=O (OCOCH <sub>3</sub> ) C=O	0.66 (t)	CH <sub>3</sub> (3H)
			1.8 (s)	OCOCH <sub>3</sub> (3H)
			3.05 (q)	CH <sub>2</sub> (2H)
			7.0-8.0 (m)	Ar (14H)
			10.26 (s)	CO <sub>2</sub> H (1H)
IX	3500-2700 (br) 1720 (s)	OH C=O	0.6 (t)	CH <sub>3</sub> (3H)
			3.57 (q)	CH <sub>2</sub> (2H)
			4.74 (s)	benzyl CH <sub>2</sub> (2H)
			6.3 (br)	alcoholic OH (1H)
			7.0-8.4 (m)	ArH, ArOH (15H)
X	3600-2800 (br) 1775 (s) 1735 (vs)	OH C=O (OCOCH <sub>3</sub> ) C=O		
XI	1720 (s)	C=O	0.62 (2t)	CH <sub>3</sub> (6H)
			3.54 (2q)	CH <sub>2</sub> (4H)
			4.45 (s)	CH <sub>2</sub> OCH <sub>2</sub> (4H)
			7.05-8.2	ArH + ArOH (30H)
XII	1770 (s) 1730 (vs)	C=O (OCOCH <sub>3</sub> ) C=O		
XIVa	3600-3300 (br) 1725 (s) 1660 (s)	OH C=O bonded C=O	0.6 (t), 0.7 (t)	CH <sub>3</sub> (6H)
			3.5 (q), 3.9 (q)	CH <sub>2</sub> (4H)
			6.7-7.4 (m)	ArOH (1H)
XIVb	1729 (s)	C=O	0.6 (t), 0.9 (t)	CH <sub>3</sub> (6H)
			3.4 (s)	OCH <sub>3</sub> (3H)
			3.6 (q), 4.0 (q)	CH <sub>2</sub> (4H)
			6.9-7.6 (m)	ArH (14H)
XIVc	1770 (s) 1728 (vs)	C=O (OCOCH <sub>3</sub> ) C=O	0.6 (t), 0.8 (t)	CH <sub>3</sub> (6H)
			1.85 (s)	OCOCH <sub>3</sub> (3H)
			3.6 (q), 3.9 (q)	CH <sub>2</sub> (4H)
			6.7-7.4 (m)	ArH (14H)

TABLE I (Continued)

Compound	$\nu$ max/cm <sup>-1</sup>	$\delta$	Protons (b)
ethyl salicylate	3500-3050 (br)	1.4 (t)	CH <sub>3</sub> (3H)
	1675 (bs)	4.2 (q)	CH <sub>2</sub> (2H)
		6.4-7.6 (m)	ArH (4H)
		10.6 (s)	ArOH (1H)
Salicylic acid (a)	3400-2400 (br)	6.6-8.0 (m)	ArH (4H)
	1660 (vs)	10.6 (s)	ArOH, CO <sub>2</sub> H (2H)

(a) Ir spectra in Nujol and nmr spectra in deuteriodimethylsulphoxide. (b) ArH represent protons of the phenyl and pyridyl groups. Carboxylic and phenolic protons are exchangeable.

TABLE II

## Analytical Results

Compound	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
III	C <sub>29</sub> H <sub>25</sub> NO <sub>5</sub>	74.61	5.35	3.00	74.54	5.27	3.09
IV	C <sub>30</sub> H <sub>27</sub> NO <sub>5</sub>	74.84	5.61	2.91	75.00	5.61	2.92
V	C <sub>31</sub> H <sub>27</sub> NO <sub>6</sub>	73.08	5.3	2.75	72.94	5.09	3.10
VI	C <sub>27</sub> H <sub>21</sub> NO <sub>5</sub>	73.80	4.78	3.19	73.63	4.71	3.11
VII	C <sub>29</sub> H <sub>25</sub> NO <sub>5</sub>	74.61	5.35	3.00	74.38	5.66	3.00
VIII	C <sub>29</sub> H <sub>23</sub> NO <sub>6</sub>	72.35	4.87	2.91	72.35	5.21	2.79
IX	C <sub>27</sub> H <sub>23</sub> NO <sub>4</sub>	76.24	5.41	3.29	76.38	5.66	3.21
XI	C <sub>54</sub> H <sub>44</sub> N <sub>2</sub> O <sub>7</sub>	78.29	5.44	3.36	78.31	5.47	3.37
XIVa	C <sub>30</sub> H <sub>25</sub> ClO <sub>5</sub>	71.93	5.00	—	71.71	4.94	—
XIVb	C <sub>31</sub> H <sub>27</sub> ClO <sub>5</sub>	72.3	5.25	—	72.29	5.36	—
XIVc	C <sub>32</sub> H <sub>27</sub> ClO <sub>6</sub>	70.78	4.98	—	70.69	4.92	—

(Table I). It was found that during melting point determination of the alcohol IX, another solid compound was formed and remelts again at higher temperatures. Therefore a sample form IX was heated over its melting point for a few minutes and the new solid compound which was obtained in very good yield was purified and analysed. Elementary analyses results indicated that the compound thus formed was in fact the outcome of the combination between two molecules of the alcohol IX with a loss of a molecule of water. The latter product was identified as an ether and its structure was assigned as XI on the basis of spectral evidences (Table I). It has been reported that similar ether formation from saligenin (salicyl alcohol) was obtained by heating the latter with a large excess of ethanol in a sealed tube at 150° (8). The acetoxy derivatives X and XII of both IX and XI were also prepared.

From the above reactions on compound III it is concluded that as the salicylate part of the molecule is the reactive center toward different reagents, the ester group which is *para* to the phenolic group is rather inert.

## EXPERIMENTAL

Unless otherwise stated, ir spectra were measured with Beck-

man IR 10 instrument for solutions in chloroform, <sup>1</sup>H nmr spectra with Varian T-60A instrument for solutions in deuteriochloroform containing tetramethylsilane as the internal standard. Microanalytical samples were analysed using 185B HP CHN analyzer 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 Ethyl 3-Pyridylacetate.

Ethyl 3-pyridylacetate (8.8 g.) and ethyl phenylpropiolate (9.3 g.) were added successively to a suspension of sodium ethoxide (3.5 g.) in dry ether (200 ml.). The reaction mixture, which gradually became deep red was kept overnight at room temperature and then refluxed for two days. The mixture was poured into water and extracted with ether. The ethereal extract was dried (magnesium sulfate) and evaporated to give a brown oil (9.0 g.). The aqueous layer was acidified with dilute acetic acid to pH 7 and then extracted with ether. The ethereal extract was washed with sodium bicarbonate solution, dried (magnesium sulfate) and evaporated to give ethyl 3,5-diphenyl-4-carboxy-6-(3-pyridyl) salicylate (III) as a white solid product (4.4 g.), m.p. 138-140° (from acetone). More of this compound (2.8 g.) was obtained by treatment of the above brown oil with ether, total yield, 58%. 2,4-Dicarboxy-3,5-diphenyl-6-(3-pyridyl)anisole (IV).

A solution of compound III (0.5 g.) in ether was mixed with an ethereal solution of diazomethane. The product (IV) was obtained after evaporation of the solvent as pale yellow crystals (0.45 g.),

m.p. 141-143° (from ether), yield, 87.4%.

Ethyl 3,5-Diphenyl-4-carbomethoxy-6-(3-pyridyl)acetylsalicylate (V).

Compound III (0.25 g.) was added to a mixture of acetic anhydride (0.25 g.) and anhydrous sodium acetate (0.05 g.). The reaction mixture was refluxed on a water bath for one hour, cooled and then cold water was added. The product (V) was obtained as a white solid (0.26 g.), m.p. 149-150° (from ethanol), yield, 95.4%.

3,5-Diphenyl-4-carbomethoxy-6-(3-pyridyl)salicylic Acid (VI).

Compound III (0.7 g.) was added to a solution prepared by successive addition of methanol (7.0 ml.) and water (0.0 ml.) to sodium (0.7 g.). The mixture was refluxed for two hours, cooled and filtered. Acidification of the sodium salt thus formed with dilute sulfuric acid (10%) and filtration afforded the product (VI) as a white solid (0.45 g.), m.p. 234-236° (from ethanol), yield, 95.9%. The chloroform solution of the product formed a greenish copper complex when treated with an aqueous solution of copper acetate.

3,5-Diphenyl-4-carbomethoxy-6-(3-pyridyl)acetylsalicylic Acid (VIII).

Compound VI (0.5 g.) was acetylated as mentioned for compound V to give a white solid (0.45 g.), m.p. 192-193° (from methanol), yield, 82.1%.

3,5-Diphenyl-2-carbomethoxy-4-carbomethoxy-5-(3-pyridyl)anisole (VII).

Compound VI (0.1 g.) dissolved in methanol (10 ml.) and ether (100 ml.) was treated with excess of ethereal diazomethane and then allowed to stand overnight. The reaction product was worked up to give compound VII (0.1 g.), m.p. 142-144° (from ether), yield 96.9%.

4,6-Diphenyl-5-carbomethoxy-3-(3-pyridyl)-2-hydroxybenzyl Alcohol (IX).

Compound III (0.8 g.) in dry ether (100 ml.) was added dropwise, with stirring and under nitrogen atmosphere, to a solution of lithium aluminium hydride (0.2 g.) in dry ether (100 ml.). The mixture was refluxed for one hour, cooled, acidified with dilute sulfuric acid (10%) and then extracted with ether. The ethereal extracts were worked up to give compound IX as a light white solid (0.62 g.), m.p. 98-100° (from ether-light petroleum ether), yield, 85.1%. The corresponding acetoxy derivative (X) was prepared as mentioned for compound V.

4,6-Diphenyl-5-carbomethoxy-3-(3-pyridyl)-2-hydroxybenzyl Ether (XI).

Compound IX (0.5 g.) in ethanol (10 ml.) was heated in an oil bath at 100-110° for one hour. Filtration gave compound XI as a bright white solid (0.4 g.), m.p. 218-219° (from methanol), yield, 83.3%. The corresponding acetoxy derivative (XII) was prepared as mentioned for compound V.

2,4-Dicarbomethoxy-3,5-diphenyl-6-(*p*-chlorophenyl)anisole (XIVb).

A solution of compound XIVa (0.3 g.) in 5% sodium hydroxide (20 ml.) was treated with dimethyl sulfate (1 ml.). After cooling, compound XIVb was isolated (0.26 g.), m.p. 166-167° (from methanol), yield, 83.9%.

Ethyl 3,5-Diphenyl-4-carbomethoxy-6-(*p*-chlorophenyl)acetylsalicylate (XIVc).

Compound XIVa (0.3 g.) was acetylated as mentioned for compound V to give compound XIVc (0.28 g.), m.p. 165-166° (from methanol), yield, 84.9%.

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